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RADIOLOGICAL HEALTH RESEARCH

SUMMARY REPORT

JULY 1965 - DECEMBER 1966

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service

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U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Bureau of Disease Prevention and Environmental Control
National Center for Radiological Health

RADIOLOGICAL HEALTH RESEARCH

Summary Report July 1965 - December 1966

Rockville, Maryland

PREFACE

The work reported in this document reflects the activities of the Research Branch of the Division of Radiological Health, Public Health Service, prior to the extensive reorganization of the Service which became effective in January 1967. The Division of Radiological Health has been reorganized and renamed the National Center for Radiological Health; it is one of several Centers in the new Bureau of Disease Prevention and Environmental Control.

Although the mission of the new Center remains essentially unchanged, considerable administrative reorganization has been effected. Each of the Sections of Research Branch, as described in this report, has been detached and new programs have been established. Most of the Radiobiology Section has been included in the new Radiation Bio-Effects Program, Epidemiology Section forms part of the new Population Studies Program, and the Environmental Sciences Section has become part of the Environmental Surveillance and Control Program.

This document summarizes the work of the old Research Branch during its last 18 months. To present this information in light of the new organization would have required considerable rewriting and delayed publication. As in the past, the results of work in the new Programs will be reported at scientific meetings, in the open literature, and in Government publications.

James G. Terrill, Jr.

James G. Terrill, Jr.
Director
National Center for Radiological Health

FOREWORD

Since its establishment in 1958, the Division of Radiological Health has been responsible for developing a comprehensive radiological health program in the Public Health Service. The Division has conducted an active program designed to prevent, reduce, or ameliorate the adverse effects of radiation exposure to the population while achieving optimum benefits from radiation science and technology.

To support these objectives, the Research Branch of the Division administered Public Health research programs covering (1) investigation of the biological effects of radiation, (2) development of data upon which radiation exposure standards can be based, (3) investigation of the long-term effects of radiation dose and disease occurrence in human population groups, and (4) development of preventive measures and specialized equipment for use in reducing environmental radiation exposure.

This report summarizes recent work of the Research Branch, and provides information under one cover that is easily accessible to those in the Public Health Service and others interested in radiological health research activities. The first few pages describe in a general way the Branch mission, goals, and physical facilities; the body of the report summarizes Branch projects and the achievements made during the past 18 months. The organization of Research Branch and the publications and presentations by Branch authors are given in the appendixes.

Arthur H Wolff

Arthur H. Wolff, Chief
Radiation Bio-Effects Program
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(formerly Chief, Research Branch,
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I. INTRODUCTION

A. RESEARCH BRANCH, ITS PLACE IN THE DIVISION

The Division of Radiological Health, established by the Surgeon General in 1958, supports research relating to the control of radiation hazards; provides technical assistance to states and localities; develops, through research studies, and in consultation with federal, state, and local agencies, uniform standards of radiation protection; and provides training for professional and technical persons in matters relating to radiation hazard control. The Division carries out these functions in four branches--State Assistance Branch, Technical Operations Branch, Training Branch, and Research Branch.

Research Branch is responsible primarily for (i) determining, through various experimental and epidemiological methods, the effects of radiation on man, and (ii) developing methods for reducing and controlling radiation exposure. The Branch program is actively pursued in experimental and field laboratories administered by the Division, and through contracts with universities, medical centers, and other public and private institutions that have particular facilities or competence to conduct research of vital interest to the Branch.

Since its establishment the Division has grown considerably. The National Advisory Committee on Radiation, in its original report to the Surgeon General, recommended "that the program be developed gradually, perhaps at a level of approximately $2,500,000 in the fiscal year 1959-60 and increase in magnitude until full development is reached in 1965." The FY 1966 Division budget exceeded $20,000,000, and Research Branch was allotted about one-fifth of that amount.

Approximately 185 scientists, technicians, and supporting staff are engaged in Research Branch activities, which are organized into three major sections. Epidemiology Section is concerned with studies of populations and effects of radiation in man. The Radiation Biology Section studies the effects of radiation on experimental animals, tissues, and cells in an effort to define radiation effects in humans. The Environmental Sciences Section examines transport mechanisms in the biosphere to determine how these mechanisms may operate and be interrupted to reduce the radiation hazard to man.

B. BASIC INVESTIGATIONS

In its primary approach to determine long-term effects of radiation on man, Research Branch conducts studies of the relationships between radiation dose and the incidence of disease and disability in human population groups. Such human population studies involve identifying suitable study groups that have a common source of definable radiation exposure, determining the radiation dose received by members of groups, and comparing disease and disability indices between the study group and suitable controls. In addition, field and laboratory supportive studies are carried out to develop sensitive methods, techniques, and epidemiologically useful tools to detect and interpret biologic damage related to low-level radiation exposures.

Two types of laboratory studies provide a firm basis for the epidemiologic studies. The first type is used to develop indices of radiation damage that can then be applied to the human population studies. Such laboratory studies can also provide information on mechanisms of radiation damage, which lead not only to a better understanding of radiation effects, but also may lead to methods by which radiation damage can be diagnosed early, prevented, mitigated, or treated. The second type, laboratory and related field studies, is designed to provide a firm basis for estimating body burdens and radiation doses so that studies of human population groups may yield, as precisely as possible, quantitative relationships between radiation dose and effect.

Studies of biochemical and structural cellular changes resulting from radiation exposure involve tissue and organ systems. Cell and tissue culture techniques have been developed and promise leads that can be exploited to define the mechanism by which radiation injury is transmitted to succeeding generations of cells. Experiments designed to define relationships between radiation sensitivity and age at the time of exposure have begun at Colorado State University using a large colony of dogs as experimental animals.

Studies of human chromosomal changes following diagnostic X rays and other types of exposure have been extended to various age groups. In addition, biochemical measurements of DNA-related changes are being studied to provide indices of radiation effects in human population groups which are more sensitive than mortality and morbidity statistics currently used.

The Branch investigates the occurrence and movement of radionuclides from their source to their eventual deposition in man, in order to identify points at which intervention to reduce ultimate exposure would be most feasible and effective. The Branch also studies the safety, feasibility, and effectiveness of various measures designed to prevent radionuclide contamination.

The studies just mentioned are broad investigations on which Research Branch places primary emphasis. Supporting these broad investigations are numerous projects; synopses of most projects are presented in Sections III, IV, and V of this report. Generally, the summaries are placed into groups that coincide with the administrative sections of the Branch: Radiation Biology, Epidemiology, and Environmental Sciences.

II. FACILITIES

The Division operates five laboratories located in various parts of the United States. Each of the laboratories conducts projects directed by Research Branch (as well as projects of other Branches) through officers in charge of each laboratory. Some projects are carried on entirely within one laboratory and other projects are cooperative efforts conducted at more than one laboratory.

A. TWINBROOK LABORATORY

The administrative offices of Research Branch are located in the Twinbrook Laboratory building in Rockville, Maryland. The offices also serve as the headquarters for wide-ranging epidemiological studies on groups of people who have received certain medical radiation exposures, and populations that have been exposed to natural and man-made radiation in the environment.

The Branch activities in Rockville were highlighted last year by the dedication of the Twinbrook Laboratory on January 25, 1966 (Figures 1, 2). Deputy Surgeon General Leo J. Gehrig represented the Surgeon General at the dedication. Division of Radiological Health Chief Donald R. Chadwick described the Branch goals and commented on the new facilities. An open house followed the ceremonies.

The Twinbrook Laboratory is the first Government Laboratory devoted exclusively to radiological health research. Most of the space in the new building is occupied by an active radiobiology research program that supports Division studies on the long-term biological effects in human population groups. The cytogenetic, biophysical, biochemical, radiochemical, and pathological studies are supported by an experimental animal colony, electron microscopic facilities, and irradiation, dosimetric, and counting facilities.

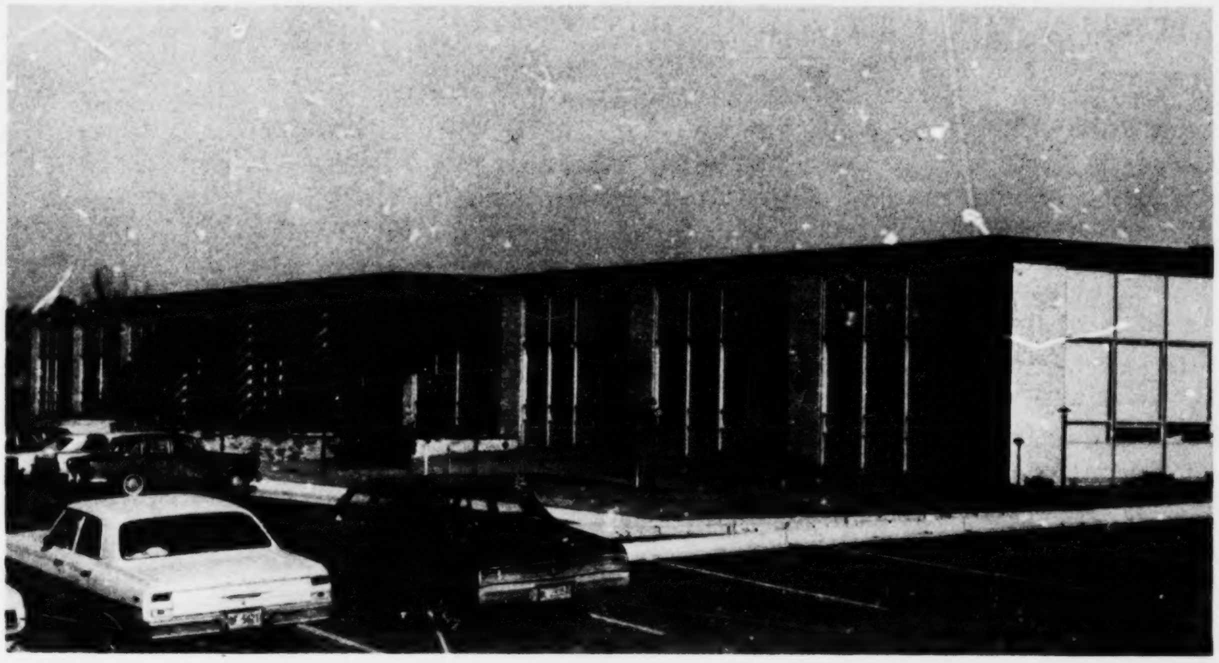

Figure 1. Twinbrook Research Building, Rockville, Maryland.

Figure 2. Deputy Surgeon General Leo J. Gehrig (left) and DRH Chief Donald R. Chadwick Discuss the Facilities at the Dedication of the Twinbrook Laboratory.

B. ROBERT A. TAFT SANITARY ENGINEERING CENTER

The oldest laboratory facilities in the Division are those located at the Robert A. Taft Sanitary Engineering Center in Cincinnati, Ohio (Figure 3). As early as 1952 radiation training activities were carried out there. Subsequently, broader radiological training activities, improved methods for analyzing samples, broader radiological safety programs, plans for a surveillance network, and other programs basic to the Division mission were developed at that laboratory.

With the establishment of the Division of Radiological Health in 1958, many of the radiological activities were shifted from Cincinnati to other laboratories. However, the Taft Sanitary Engineering Center remains one of the most active laboratories in the Division and employs about 50 persons in Radiological Health Research Activities (RHRA). These persons not only explore methods for counting radioactivity, calibrating instruments, evaluating analytical procedures, and calibrating and maintaining whole-body counters; but they also provide biometric support for Division activities and conduct a number of projects associated with both Radiobiology and Environmental Sciences Sections. In addition, programs in nuclear engineering and nuclear medicine have recently been established here.

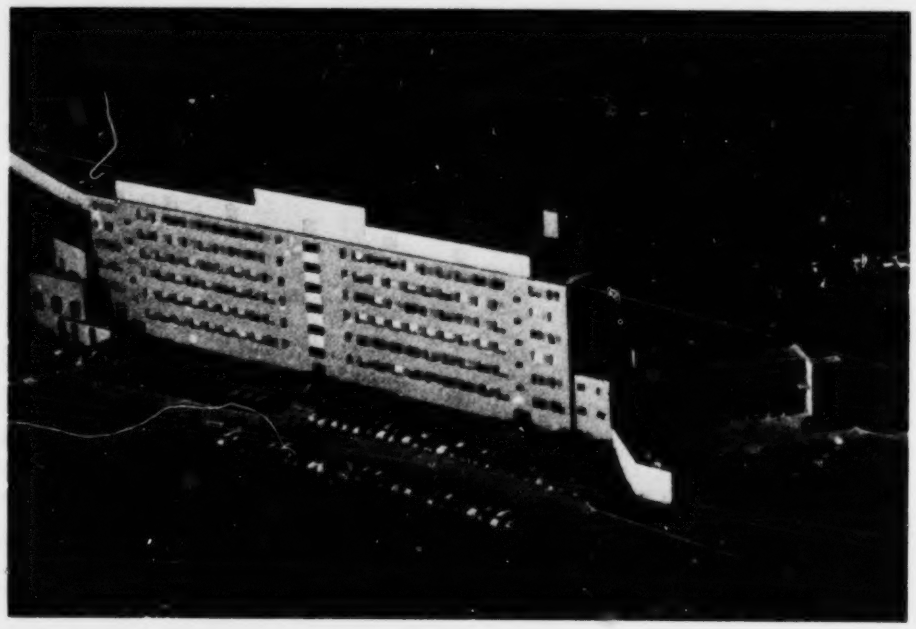

Figure 3. Robert A. Taft
Sanitary Engineering Center,
Cincinnati, Ohio.

C. SOUTHEASTERN RADIOLOGICAL HEALTH LABORATORY

The Southeastern Radiological Health Laboratory (Figure 4) was established in Montgomery, Alabama, in 1960. The laboratory fosters radiological surveillance programs in the Southeastern United States, performs research on the effects of low levels of external and internal radiation on biological systems, and provides technical assistance to other health agencies through training, consultation, and laboratory support.

During the year new bionomical investigations have begun here. These investigations will trace radionuclide transport from the atmosphere, through the soil, into plant systems, and ultimately into the human body. Soil types, plant species, and various environmental factors will be considered. Expanded facilities are being planned at SERHL to support these studies.

Arrangements are being made to keep two milk decontamination plants at SERHL. One is a commercial-scale plant that has proved the feasibility of removing radioactive iodine and strontium from milk. This plant has been dismantled and shipped to SERHL. Further work on this decontamination process will be done at SERHL. The other plant removes radionuclides from milk by a slightly different process and is presently being tested. It fits in a standard truck trailer, and will be used in further milk decontamination studies at SERHL.

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PUBLIC HEALTH SERVICE
SOUTHEASTERN RADIOLOGICAL
HEALTH FACILITY

Figure 4. Entrance to Southeastern Radiological Health Laboratory, Montgomery, Alabama.

D. NORTHEASTERN RADIOLOGICAL HEALTH LABORATORY

The Northeastern Radiological Health Laboratory building (NERHL) in Winchester, Massachusetts, was turned over to the Public Health Service from the Atomic Energy Commission in the fall of 1961, making this laboratory the most recent one to come under DRH administration (Figure 5).

The major efforts of the Research Branch at this facility revolve around the Thorotrast study. Its aim is to describe the radiologically significant effects thorium dioxide might have had on persons who received it as a contrast medium for X-ray diagnoses in the years 1930 to 1950.

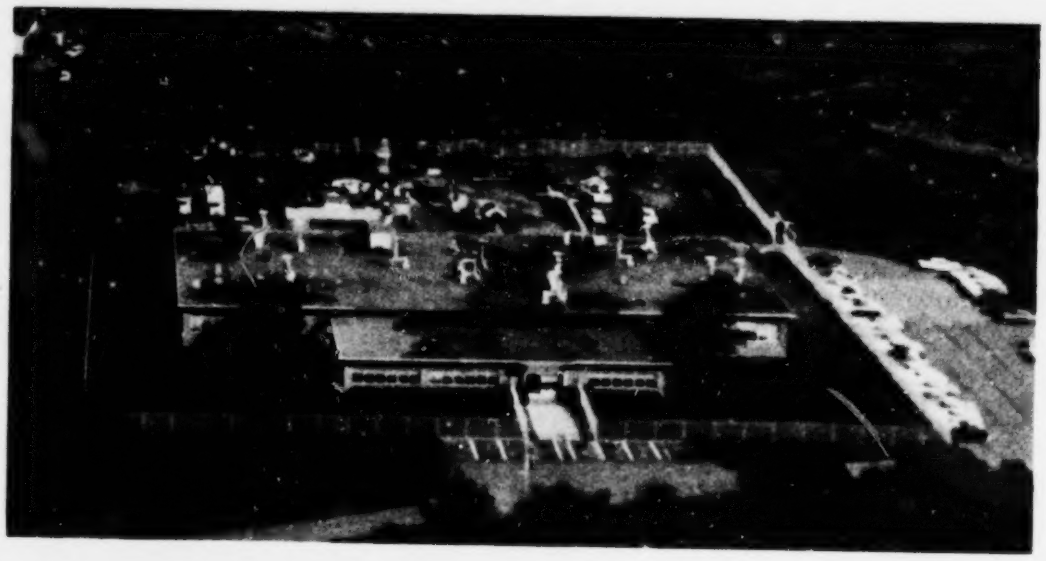

Figure 5. Aerial View of the Northeastern Radiological Health Laboratory, Winchester, Massachusetts.

E. SOUTHWESTERN RADIOLOGICAL HEALTH LABORATORY

On July 7, 1966, approximately 600 people witnessed the official dedication of the new SWRHL laboratory (Figure 6). Dr. Donald R. Chadwick, Chief of the Division of Radiological Health, introduced many distinguished speakers and guests including Assistant Surgeon General Dr. Richard A. Prindle and Nevada's Senator Alan E. Bible, and Governor Grant Sawyer.

Following the dedication ceremonies, the public was invited to tour the new buildings and view the special exhibits. On July 8 and 9, more than 25 papers were presented at a well-attended technical seminar on "New Developments in PHS Radiation Surveillance and Environmental Sciences Research."

The new facilities and those planned will permit broad investigations into methods of controlling and reducing radioactivity in the environment. Research Branch studies at the Nevada laboratory are directed toward the understanding of human radionuclide exposure-dosage relationships resulting from a variety of field release conditions. Many of these studies are carried out in conjunction with the Atomic Energy Commission.

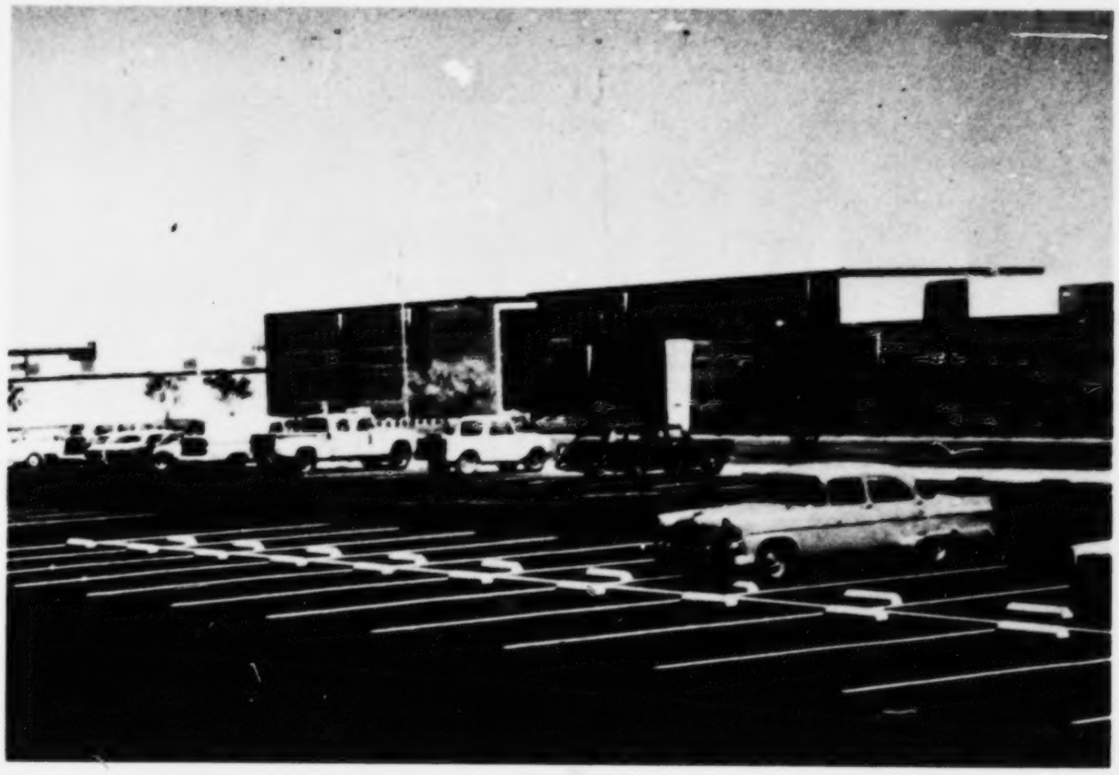

Figure 6. Southwestern Radiological Health Laboratory, Las Vegas, Nevada.

F. COLLABORATIVE RADIOLOGICAL HEALTH LABORATORY, COLORADO STATE UNIVERSITY

In 1961 the Division of Radiological Health and Colorado State University initiated a collaborative effort to investigate the long-term effects of low-level exposure to radiation. Beagles were the animals of choice for the experiments, and a general long-term protocol was established. One laboratory facility and a number of kennels were constructed on the "Foothills Campus" a few miles from the main CSU campus at Fort Collins. The building provides facilities for working with small laboratory animals within a "specific pathogen free" colony. Persons entering the laboratory must shower and change clothes, and all equipment and supplies are sterilized before being brought into the laboratory.

During this year 600 kennels were completed and construction of 700 additional pens was begun. Two animals are housed per pen, thus there will be kennels for more than 2,000 experimental animals in addition to those maintained for breeding (Figure 7).

The new Radiation and Environmental Stresses Building was completed during the year and dedicated in October 1966. This new facility was built with National Institutes of Health funds and provides space for research in other environmental problems including aspects directly related to the CRHL project.

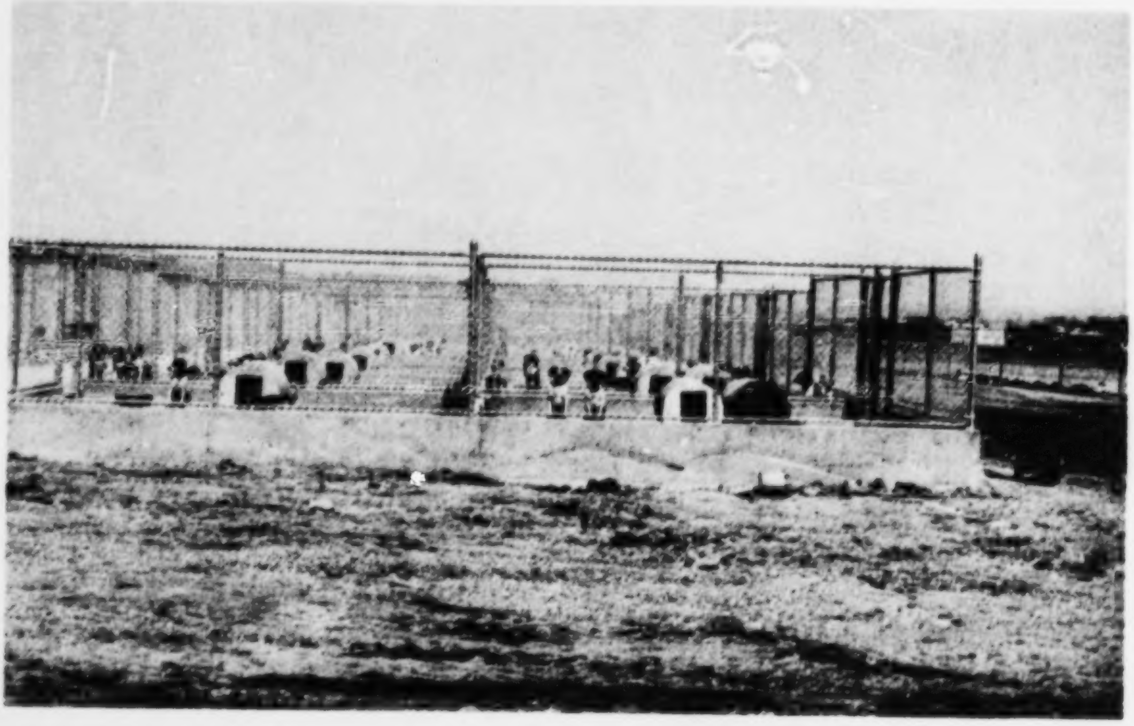

Figure 7. Kennels at the Collaborative Radiological Health Laboratory Will Accommodate Approximately 2,000 Dogs.

III. RADIATION BIOLOGY

The radiobiology investigations are the most diverse of the Branch. They range from molecular, ultrastructural, and cytogenetic investigations to physiologic and gross pathologic studies. The responses of various in vivo and in vitro systems to radiation are under study at the Branch facilities and elsewhere under contracts to determine dose-radiation relationships of importance in man.

A. BIOPHYSICAL INDICATORS OF RADIATION DAMAGE

Considerable evidence supports the thesis that the deleterious effects of ionizing radiation in living organisms is attributable to physicochemical changes at the cellular and subcellular levels. The functions of organized cell systems depend upon normal metabolic activity within cells. Metabolic activity involves protein synthesis and ultimately the integrity of biologically important molecules such as DNA, RNA, and proteins, including enzymes. An alteration in the metabolic control chain within cells may produce alterations in the function of organized cell systems. Studies to define these effects may provide sensitive indicators of radiation-induced damage to living organisms.

1. Protein Synthesis in Normal and Irradiated Cells

a. Hormonal Effects on In Vitro Protein Synthesis

W. A. Mills

Protein synthesis is thought to be controlled by hormones that unblock the DNA template allowing new RNA synthesis and subsequent formation of specific enzymes. The influence of thyrotropic stimulating (TSH), follicle stimulating (FSH), and luteinizing (LH) hormones of the anterior pituitary gland on protein synthesis was investigated in a cell-free system obtained from rabbit reticulocytes. The incorporation of carbon-14 labeled amino acids was stimulated either by native messenger RNA alone (mRNA) or by native mRNA plus polyuridylic acid (poly U).

Figure 8 shows the effects of different concentrations of TSH on the incorporation of carbon-14 phenylalanine into protein by both native messenger RNA and an added 50 μg of poly U per milliliter of reaction mixture. Protein synthesis decreased at concentrations as low as 0.01 unit TSH per milliliter of reaction mixture (20 times human plasma levels). Similar results were found with FSH and LH.

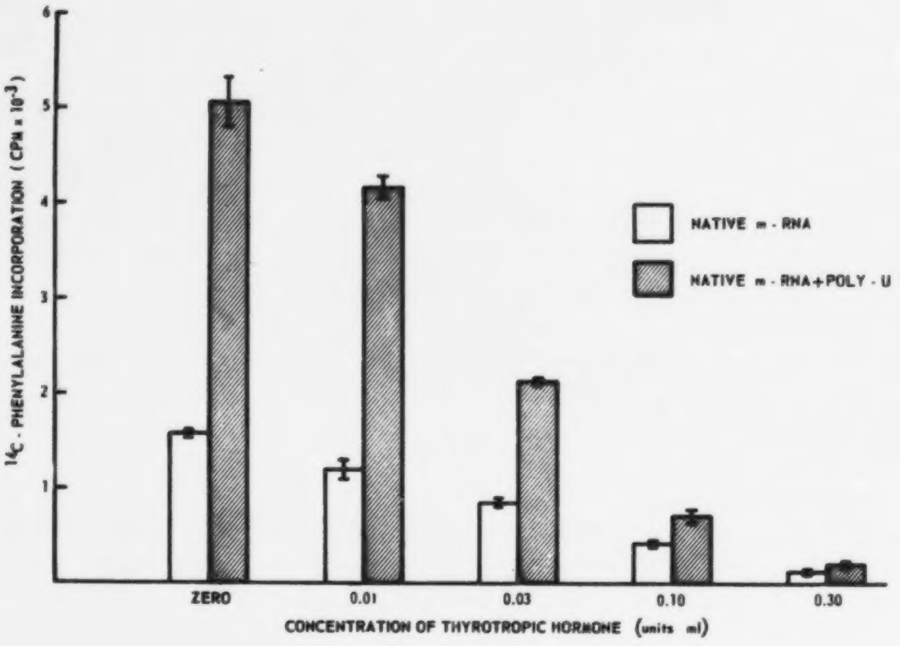

Figure 8. Effects of Thyrotropic Hormone on Phenylalanine Incorporation into Protein.

Experiments to determine the effect of incubation time on the amount of protein synthesized showed that at 37° C about 50% of the total amino acid incorporation over a 60-minute incubation period occurs within the first 15 minutes of incubation. This finding was consistent with results which indicated that most of the inhibition with TSH occurs within the first 15 minutes of protein synthesis.

Additional experiments showed the TSH "inhibition factor" to be nondialyzable and nonspecific for the type of amino acid incorporated into protein. Also, it was found that proteins such as bovine serum albumin and bovine gamma globulin have no effect on protein synthesis in this system even at concentrations many times the protein concentration of the hormones investigated.

Current studies are in progress to determine if irradiation of various components of the cell-free system or radiation exposure of rabbits, as the source of reticulocytes, influences these observed effects of hormones.

b. Inhibition by Actinomycin D on the Induction of Tryptophan Pyrrolase by Hydrocortisone

E. P. Mishkin, M. L. Shore

It has been demonstrated that the activity of the enzyme tryptophan pyrrolase in rat liver can be increased by the administration of tryptophan as well as by injection of cortisone. It is now generally accepted that hydrocortisone gives rise to *de novo* synthesis of the enzyme, and that some other mechanism, most probably enzyme stabilization, leads to increased levels of enzyme following tryptophan administration.

In the present study an effort was made to confirm the reported observation that actinomycin (an antibiotic generally believed to interfere with messenger RNA synthesis), given during the induction of tryptophan pyrrolase by hydrocortisone, appears to facilitate rather than interfere with the synthesis of this enzyme. The effect of actinomycin on enzyme induction was tested throughout the enzyme induction period for as long as 24 hours after hydrocortisone administration. At no time did actinomycin enhance normal enzyme induction. This study suggests that actinomycin either decreases or is without effect on induced enzyme synthesis. This agrees with current concepts on the mechanism of action of actinomycin and makes it unnecessary to invoke the concept of a tryptophan pyrrolase mRNA repressor that is operative at the level of mRNA translation.

c. Interference with the Induced Synthesis of Tryptophan Pyrrolase by X Irradiation

E. P. Mishkin, M. L. Shore

In a previous study it was demonstrated that 180 rads of X rays administered on day 15 of gestation altered the development of enzyme activities in newborn rats. This dose interfered with normal increases in the activities of lactic and glycerophosphate dehydrogenases, and glucose-6-phosphatase, which occur at birth. However, the mechanisms involved in the development of this abnormality are not well understood and may have been indirect.

To provide direct evidence of the possible interaction between radiation and nucleoproteins and the expression of this interaction in terms of altered enzyme synthesis, experiments were performed involving the inducible enzyme, tryptophan pyrrolase. The hormonal induction of this enzyme is known to require the synthesis of new messenger RNA. Substrate induction of this enzyme by tryptophan is generally believed to result from other mechanisms, which probably involve enzyme stabilization and continued synthesis of enzyme at a basal rate.

Food- and water-deprived animals were irradiated (800 rad) or sham-irradiated. Either hormonal or tryptophan enzyme induction was attempted 24 hours later. X irradiation interfered with the normal induction of the enzyme 5 hours after hydrocortisone injection (Figure 9), and 9 hours after tryptophan injection (Figure 10).

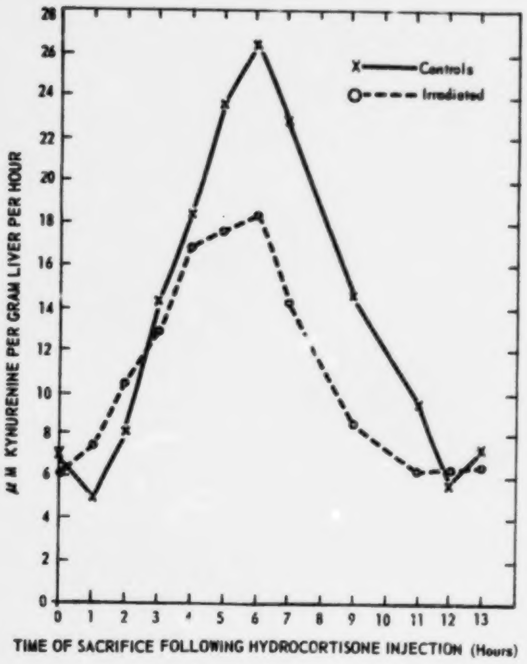

Figure 9. Comparison of Tryptophan Pyrrolase Levels Following Injection of Hydrocortisone in Actinomycin-Treated and Control Rats.

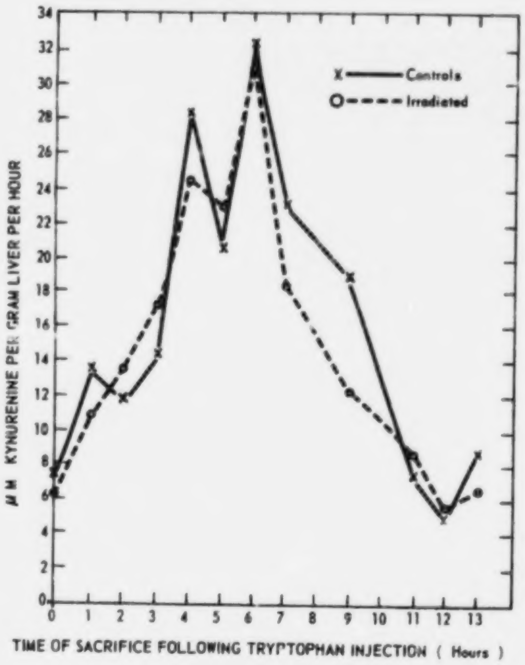

Figure 10. Enzyme Induction Curves in Irradiated and Control Animals After Tryptophan Injection.

The delayed radiation effect, coupled with induction to levels that did not appear to be attainable on the basis of enzyme stabilization and basal enzyme synthesis, suggested that substrate induction may also depend on the synthesis of new mRNA. Experiments were therefore performed to determine whether the kinetics of tryptophan induction would be altered by actinomycin D. Actinomycin decreased substrate induction significantly (Figure 11). However, the experiments indicated evidence for new mRNA only after a delay of 3 hours following tryptophan administration. Thus, the decreased enzyme in liver of irradiated rats 8-10 hours after tryptophan administration may be a reflection of interference with enzyme synthesis that depends on new mRNA synthesis. A radiation effect on the induction of tryptophan pyrrolase seems to occur only when interference with the appearance of biologically effective mRNA can be implicated.

These findings are consistent with a direct effect of radiation on DNA transcription in liver cells. However, the possible role of other factors such as indirect hormone interference with protein synthesis, or mechanisms involving no changes in nucleoprotein structure must also be considered and are under investigation.

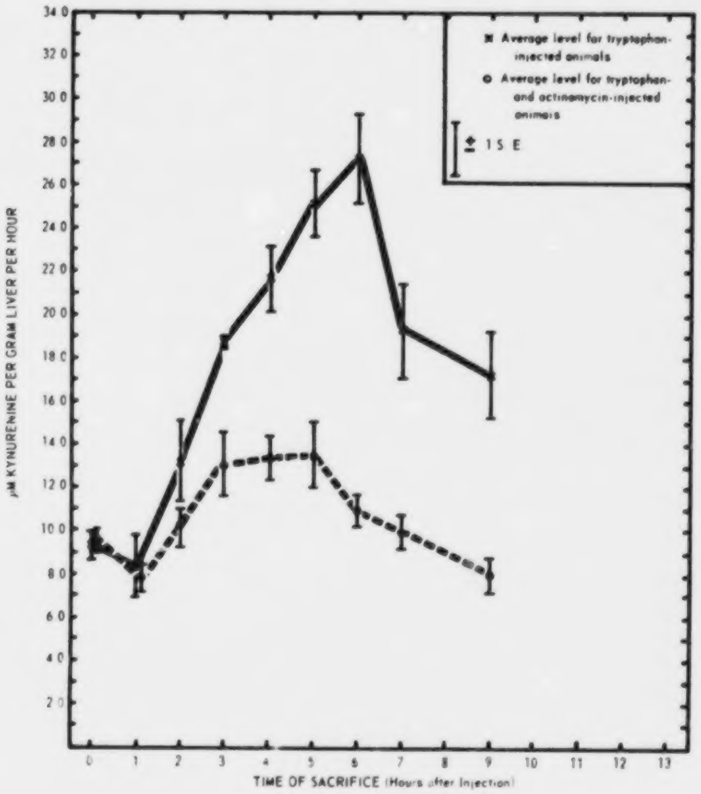

Figure 11. Tryptophan Pyrrolase Levels Following Injection of Hydrocortisone in Actinomycin-Treated and Control Rats.

2. Radiation Effects on Bioluminescence
B. H. Bruckner, A. N. Mikalis

Bacterial luminescence is of interest in radiobiology research because the biochemical reactions involved are simpler analogs of the electron-oxidative-transport systems that are essential for growth, reproduction, and energy utilization in higher creatures, including mammals. Light intensity provides a sensitive means for measuring the biological effects of radiation in these systems, and may provide insight into radiation effects in higher organisms.

In these investigations, carrier-free phosphorous 32 was incorporated into the culture medium of the luminescent microorganism *Photobacterium phosphoreum* at concentrations producing approximately 150, 300, 600, and 1,200 rad within the first generation time (60 minutes). The peak bioluminescence of the cultures increased as much as 57% under some conditions. No increased luminescence was observed in suspensions that had been X-irradiated or those that contained cesium 134 or strontium 85.

The enhanced luminescence in the presence of phosphorus 32 is believed to result from increased enzyme action induced by the energetic beta emission, because experiments using 1000X concentrations of stable phosphorus showed no enhanced luminescence.

3. Organ Function of Normal and Irradiated Cells

a. Mathematical Model of Reticuloendothelial Phagocytic Function
R. K. Fred, J. G. Harris, M. L. Shore

The reticuloendothelial system (RES), in addition to other functions, plays an important part in phagocytosis. The phagocytic capacity of the system can be measured by injecting animals with measured amounts of colloidal carbon and analyzing blood samples at specified times after colloid injection. The clearance rates, calculated from the blood samples, are related to organ function.

It has been reported, and is a widely held notion, that the clearance of colloidal carbon from the circulation follows first order kinetics; i.e., $C_t = C_0 e^{-kt}$, and that the rate-constant "k" is dependent on the initial dose of colloid injected into the animal. Together these two considerations are inconsistent with the principle of first order kinetics, which requires that the rate-constant be independent of initial concentration. It is suggested, therefore, that this mathematical description of RES phagocytic function is inadequate.

Phagocytosis involves a rate-limiting interaction between the colloidal particle and the phagocytic cell surface, followed either by engulfment of the particle into the cell, or release of the particle into the circulation. In the model described here the number of binding sites for colloid on the cell surfaces constitutes the rate-limiting factor for RES phagocytosis. This contrasts with the view of other investigators who have suggested that the rate-limiting factor in phagocytosis is the availability of a plasma protein which is believed to interact with the colloidal particle prior to phagocytosis.

Figure 12 is a diagram of the model. Colloid is injected into the body blood compartment V1 where it is assumed that instantaneous mixing occurs. Blood flows to the liver, V2, where, by means of flow K4 (fraction of total liver blood flow (FLL) contacting cell surfaces), some of the colloid comes into contact with and attaches to the RE cell surface binding sites, B3. There is then a certain probability per unit time, P4, that the colloid will be engulfed, or P3, that it will be released, as indicated by the arrows. A set of three differential equations can be written to describe clearance in terms of the number of particles (C1, C2, C3) present in the corresponding compartments at any time.

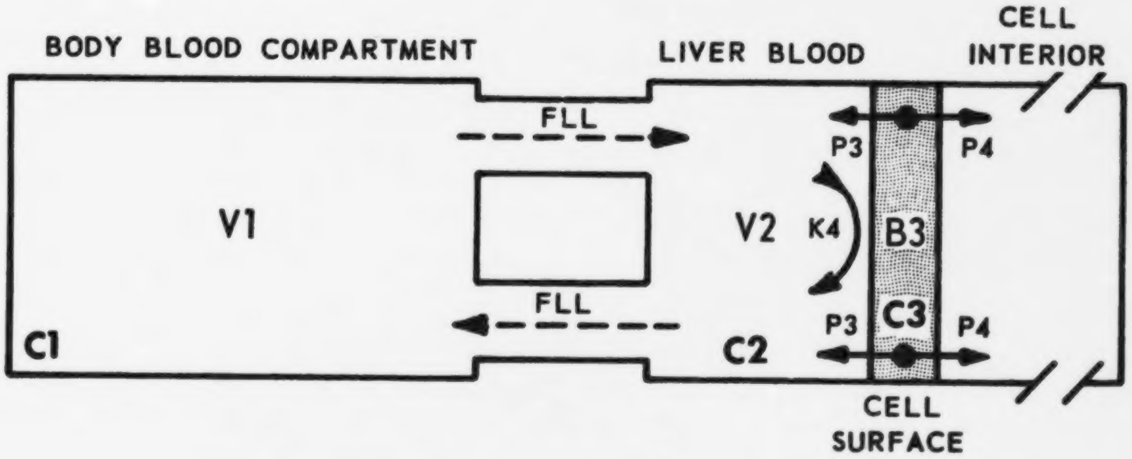

Figure 12. Diagrammatic Representation of Three Compartment Phagocytosis Model.

When a large initial dose of colloid is mathematically introduced into the body blood compartment of this system, the simulated disappearance of colloid from this compartment is initially zero order. The constant amount of colloid disappearing per unit time depends upon the probability of engulfment (P4) and the number of sites for binding of colloid on the surface of phagocytic cells (B3). Doses of colloid which are cleared in this manner are considered to be "saturating doses." Such saturating doses are predicted to force the clearance of colloid to the maximum functional phagocytic capacity of the RES.

It can be shown that at low concentrations of colloid the clearance equation reduces to first order kinetic behavior. It suggests that colloids ordinarily given in small amounts are cleared at a rate that is limited by the rate of liver blood flow.

The disappearance of an initially saturating dose of colloidal carbon was followed in the model through zero order, quasi-first order, and first order phases of colloidal clearance. Linear and semilogarithmic plots of the results were compared with typical laboratory data showing the disappearance of a large dose of colloidal carbon (18 mg/mouse). The similar characteristics of the semilogarithmic plots suggest that the rate-constant for clearance decreases as the initial dose increases. This observation corresponds to that of others, and suggests that the present RES model adequately accounts for the experimental results observed.

b. Application of a Mathematical Model to the Study of Reticuloendothelial System Phagocytosis

R. K. Fred, M. L. Shore

The proposed RES phagocytic model suggests that the amount of colloid that constitutes a saturating dose depends only upon the total number of binding sites for colloid on phagocytic cells. According to this model, the rate of clearance of a saturating dose of colloid should be dependent upon the product of the total number of binding sites and the probability of engulfment, and should not be influenced by the rate of liver blood flow.

To test these predictions experiments were performed in which the number of RE cells and the probability of engulfment were manipulated nearly independently, and the effect of such manipulations on maximum functional phagocytic capacity was noted. Figure 13b contains carbon clearance data from an experiment in which mice were previously treated with Salmonella typhosa endotoxin. Such treatment is thought to increase the phagocytic activity of existing cells which, in effect, requires that the probability of engulfment is increased. This agrees with the experimental finding that the rate of colloidal clearance in the treated mice is greater than that observed in the controls (Figure 13a). However, the 12-mg and 18-mg doses of carbon are sufficiently large to saturate the RE cell binding sites as suggested by an equal rate of disappearance. This experimental finding supports the theoretical predictions of the RES model by indicating that the probability of engulfment has increased, without a noticeable change in the number of RE cell binding sites.

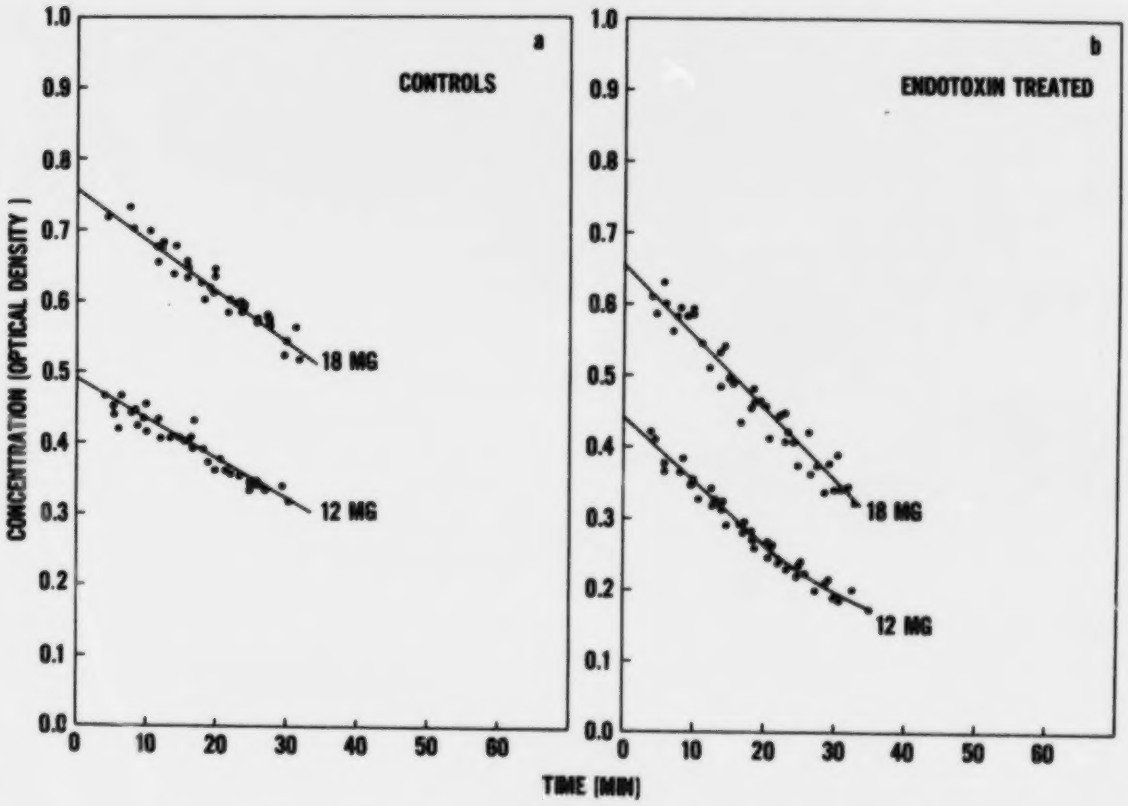

Figure 13. Clearance Curves of Control Mice (a) and Mice Treated with S. *typhosa* Endotoxin (b).

If protein synthesis were a rate-limiting factor in phagocytosis it might be expected that, under conditions in which the RES is operating at the maximum functional capacity, some effect on colloid clearance would be observed after puromycin administration. However, no difference was observed between experimental animals receiving puromycin and the controls receiving sterile water.

Figure 14 gives the results of an experiment in which the mice were treated with 1 mg of glucan 4 days before the carbon clearance was determined. Such treatment induces cellular proliferation of the RES thus increasing the total number of RE cell binding sites. The 18-mg dose of carbon is initially cleared with zero order kinetics but begins to depart from zero order behavior at a higher concentration than in the controls (Figure 13a). The 12-mg dose of carbon is no longer an initially saturating dose. These experimental results further support the prediction of the RES model by indicating that increasing the total number of binding sites increases the dose of colloid that will constitute a saturating dose.

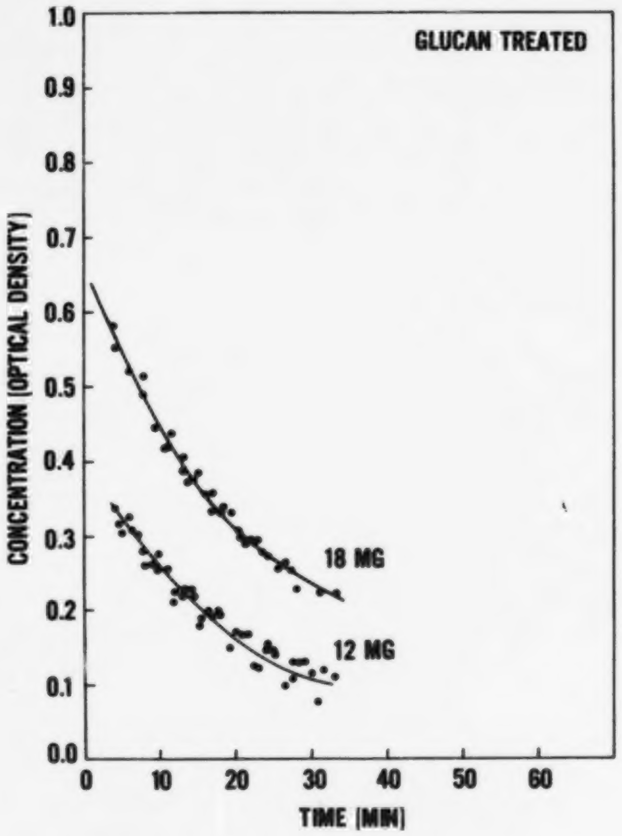

Figure 14. Carbon Clearance Curves of Glucan-Treated Mice.

c. The Proliferative and Phagocytic Capacity of the Reticuloendothelial System of Sublethally Irradiated Mice

R. K. Fred, M. L. Shore, L. S. Kelly, E. L. Dobson

It has been established that radiation reduces the proliferative response of the RES ordinarily associated with the administration of substances such as zymosan, glucan, proferin, or estradiol. On the other hand, the investigations of radiation effects on RES phagocytic function have produced contradictory conclusions.

We have investigated the effect of radiation directly on the phagocytic function of the RES. Following 700 R (20 R/min) of cesium-137 whole-body gamma irradiation, the ability of the RES to clear a large dose of intravenously administered colloidal carbon (18 mg per mouse) was significantly reduced. Previous investigations by others have ordinarily employed test doses of colloid of 6 mg or less per animal and, therefore, have not measured maximum functional capacity. We conclude that the maximum functional phagocytic capacity of irradiated mice is statistically lower than that of nonirradiated controls.

In addition we have studied the RES response to glucan in irradiated mice. Some investigators have shown that zymosan (a crude glucan) administered intravenously to mice induces proliferation of the RES in the liver with concomitant increases in RES phagocytic activity. We have found altered RES response to glucan administration following either 400 R (20 R/min), 1000 R (0.5 R/min), or 600 R (20 R/min) whole-body cobalt-60 gamma irradiation. In each case the radiation inhibits the increase in RES phagocytic activity ordinarily produced by glucan. Our experiments using sublethal radiation doses indicate that the response of the RES to glucan is more radiosensitive than previously reported.

4. Calculation of Specific Activity Time Curves in Relatively Inaccessible Compartments of a Three Compartment Kinetic Model

M. L. Shore and R. K. Fred

Radioactive tracers have been used extensively to elucidate dynamic biological processes. Their use has provided considerable insight into the turnover of elements and compounds of biological significance in the plasma and tissues of living organisms. A radioactive element or labeled compound can be injected intravenously, and its specific activity followed closely, through repeated sampling, in the plasma compartment. However, generally it is not possible to sample a tissue compartment repeatedly, and any attempt to effect such tissue sampling may perturb the system being examined.

In the present study, hypothetical experiments were performed using a computer simulated model of a three compartment open mammillary system (Figure 15). The dynamics of the system can be described by a set of three three-term exponential equations. Experimental specific activity - time curves were obtained from each of the compartments of the model after simulated introduction of a radioactive tracer into the central "plasma" compartment. Using data obtained from an independent analysis of the time curve of specific activity in the "plasma" compartment, and a single data point from each of the two "limited access" peripheral "tissue" compartments, it was possible to calculate the specific activity - time curves for each of the peripheral "tissue" compartments. Each experimentally obtained "tissue" curve was in good agreement with its respective calculated "tissue" curve, as indicated by the line-point coincidence curves shown in Figure 16. Thus, it is possible to determine specific activity curves in relatively inaccessible compartments using information available from the "plasma" compartment of the system, and a single point from each of the peripheral "tissue" compartments.

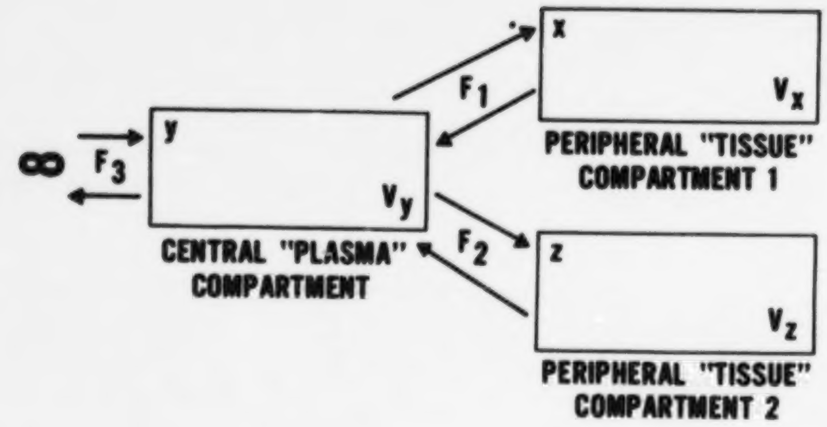
x
V_x
PERIPHERAL "TISSUE" COMPARTMENT 1
F_1
y
V_y
F_3
∞
CENTRAL "PLASMA" COMPARTMENT
F_2
z
V_z
PERIPHERAL "TISSUE" COMPARTMENT 2

Figure 15. Three Compartment Kinetic Model Used in Calculating Specific Activity - Time Curves.

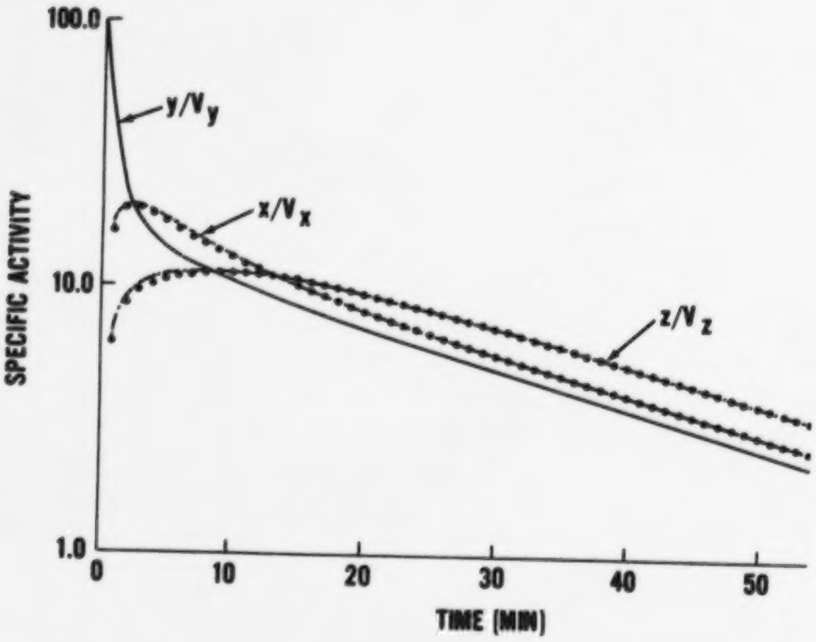

Figure 16. Specific Activity Curves in Compartments 1 and 2 Plotted with Computer Simulated Curve (y/V_y).

B. CYTOGENETIC CONSEQUENCES OF RADIATION EXPOSURE

Cytogenetic techniques provide an approach for assessing acute and long-term effects of cellular radiation damage. Such an approach permits the study of irradiation changes on one component of the cell in various types of cell populations. Comparisons of the persistence of damage in the different cell populations under study provide a measure of latent damage which may not be possible when other techniques are employed. Cytogenetic studies have demonstrated that chromosome aberrations persist many years after exposure to irradiation. Studies to determine the significance of these changes provide an excellent opportunity for furthering the knowledge of latent damage and of possible genetic damage.

1. Studies in Human Subjects

a. Radioiodine Treatment

S. Cantolino, H. Nankin

The subjects for one recent study were five adult females who had been diagnosed as being hyperthyroid and who were slated for treatment with radioiodine. None had a history of any significant radiation exposure prior to the study. A few minutes before the therapeutic oral administration of 5 mCi of iodine 131, venous blood specimens were obtained for chromosomal analysis. Subsequently, blood was drawn for chromosomal analysis at 2 hours, 1 day, 1 month, 2 months, 4 months, 6 months and 1 year after treatment. In all cases, peripheral leukocytes derived from short-term, 3-day cultures were analyzed. Only those metaphase cells were scored in which each individual chromosome could be seen and evaluated, and the chromosomes were counted in each of those scored cells. In all, more than 5,000 cells were analyzed.

In addition to the visual scoring, attempts were made to detect those aberrations that were not apparent by gross visual examination of a metaphase spread (such as small deletions and exchanges) by preparing karyotypes of at least 10 randomly selected, suitable cells for each of the time intervals studied.

The data resulting from this study indicate that therapeutic doses of radioiodine used in the management of thyrotoxicosis can cause significant and persistent chromosomal damage in peripheral leukocytes. Aberrations were detectable over the entire course of the year that these patients were observed. However, the relationship of these findings to the health of the patients cannot yet be ascertained.

b. X-Ray Treated Leukemia Patients
H. Nankin

In collaboration with the Department of Therapeutic X-ray at the NIH, a study using previously untreated patients who have documented chronic lymphocytic leukemia is in progress. These patients are receiving either 5 rads daily for 5 days or 12.5 rads twice weekly until they go into bone marrow remission or X ray is contraindicated. To date chromosomes from several patients who are currently undergoing treatment have been examined. These patients and others as they are brought into the study are to be followed for an extended period of time.

c. Radium Accident Victim

This cooperative study between the Public Health Service and the New York State Department of Health involves a 43-year-old man who received, by inhalation in 1951, a body burden of radium 226 equal to 10 to 30 percent of the maximum permissible occupational dose. Based on his whole-body count, he should be receiving an average dose to the bone of between 2.9 and 8.7 rem per year. The subject's blood is being sampled and karyotyped monthly. To investigate the occurrence in nine karyotypes of a missing "Y" chromosome, plans are being formulated to obtain a skin biopsy to determine whether this missing "Y" chromosome was lost due to mosaicism.

To aid in these chromosome studies, a simple, time-saving micromethod for culturing lymphocytes from peripheral blood has been developed. It depends on an improved culture medium and produces well-spread metaphase cells for the assessment of chromosome morphology. Only one milliliter of peripheral blood need be obtained by venipuncture; of this only seven drops are needed for culturing and harvesting. Enough well-spread metaphase cells are produced on one slide for complete analysis of the case. Parallel studies with the standard procedure shows the micromethod to be dependable.

2. Animal Studies

a. Effects of Radiation Protective and Accelerative Agents on Cultured Bone Marrow Cells
K. T. S. Yao

Preliminary experiments have been conducted to evaluate radiation protective and accelerative agents using cultured bone marrow cells from the rat kangaroo, Potorous tridactylis. In this species, the male has 13 chromosomes and the female has 12 chromosomes. The cells were treated with either 25 µg 5-bromodeoxyuridine (BUDR), 500 µg hadacidin, or 500 µg glutathione per ml of medium 6 hours before receiving 100 R of X-irradiation.

Slides made 12 hours after irradiation showed that glutathione not only had a protective effect on the cultured cells but also promoted cell growth. BUDR and hadacidin hampered cell growth and increased chromosome damage. Further experiments will be aimed at revealing the mechanism of action.

b. Chromosomal Aberrations Induced In Vitro in Chinese Hamster Cartilage and Muscle Cells

K. T. S. Yao

Chinese hamster cartilage and muscle cell cultures initiated at the Twinbrook Laboratory in January and May 1965 were used in these experiments. The cells were treated with 1 µCi of strontium 90 or cesium 134 per ml of medium for 24, 48, 72, 96, and 120 hours. At 1, 2, or 6 hours after treatment, the cells were processed to make slides for chromosome analysis. The treatments caused changes in chromosome numbers (the diploid number is 22 chromosomes), changes in chromosome structure, changes in frequency of chromosome aberration that depended on length of treatment, and changes in frequency of chromosome aberration that depended on the interval between treatment and fixation of the cells.

c. Effects of Iodine 131 on the Aberration Rate of Chromosomes from Chinese Hamster Thyroids

W. Moore

Thyroid cells of the Chinese hamster are quite sensitive to irradiation and aberrations can be demonstrated at doses to the gland as low as 6 rads. At this dose the aberration rate is increased approximately tenfold over the normal rate for the thyroid gland. Table 1 summarizes some of the more pertinent findings.

The aberrations persist for an extended time following exposure. Some of the aberrations may possibly persist for the lifetime of the animal.

TABLE 1. CHROMOSOME ABERRATIONS IN CHINESE HAMSTER THYROID CELLS

μCi ^{131}I Injected	Estimated Dose, rads	Total Cells Analyzed	Total Aberrant Cells No.	Total Aberrant Cells %
0	0	627	2	0.31
0.001	6	993	33	3.3
0.01	60	425	28	6.6
0.1	1000	455	118	25.9
0.5	5000	215	169	78.6
1.0	9900	214	198	92.5

d. A Double-Chamber Technique for Separating and Growing Mammalian Corneal Cells

K. T. S. Yao, D. Ellingson

Experiments to compare the radiation sensitivity of cells from different tissues of the same species and cell populations from different species are being conducted. Morphological and cytogenetic characteristics are the criteria for determining damage.

A double-chamber apparatus consisting of two Rose chambers is used in these studies. One Rose chamber sits on top of the other, and two plastic plates take the place of the two adjacent retaining plates. One or two holes are made on the plastic plates to hold corneas. Trypsin with a concentration of 0.25% or 0.50% in calcium and magnesium free saline solution (GKN) is used to separate epithelial and endothelial cells from the stroma. This solution is injected into the chambers which are incubated at 37° C for 30 minutes to 2 hours, or kept at 4° C overnight. Cells are harvested and cultivated in the usual medium. The non-irradiated cells from opossums, Chinese hamsters, albino rabbits, monkeys, and white rats used in these studies grew well. Epithelial cells from the X-irradiated animals would not grow, and the endothelial cells became multinucleated giant cells.

C. RADIATION PHYSICS

H. Youmans, G. E. Anderson, J. E. Barnhill, W. Lee, J. D. Manes

The Radiation Physics Unit (i) provides a complete service in Radiological Physics to the Research Branch Laboratory, (ii) conducts dosimetric research in support of the radiobiological investigators in the Laboratory, and (iii) contributes to the field of radiological physics.

Since this Unit is new to the Research Branch, most of the progress during the past year has been in obtaining a staff, designing specific programs of both service and research, and in acquiring facilities needed for the program.

1. Laboratory Service of the Radiation Physics Unit

The Radiation Physics Unit provides facilities for research requiring both external and bio-systemic sources of ionizing radiation. The radionuclide preparation room includes an absolute-filtered fume hood, glove-box, and shielded storage. Shipments of concentrated radioisotopes are received in this area and primary dilutions are made before general usage elsewhere in the laboratory.

A tracer-level counting room is equipped with a liquid scintillation spectrometer, two dual-channel gamma spectrometers, and a gas-flow geiger-proportional counter; all of these systems have automatic sample changers and printed or punched readout capabilities. The irradiation area includes a 1000 Curie cesium-137 irradiator, a 250 kv(cp) X-ray machine, and a 120 kv(p) X-ray machine.

2. Dosimetry Study of Natural Background, Kerala, India

The southern coastal regions of India have large monozite deposits that contain thorium and its daughters. The quantity may be sufficient to increase the background radiation exposure to some of the population to 30 R to 45 R per person per 30 years. This amount is an order of magnitude higher than the usual background encountered and may double the mutation rate in such areas. In a cooperative effort with the Medical College, Trivandrum, Kerala, the Radiation Physics Unit has provided two sets of lithium fluoride dosimeters.

The first set was obtained commercially and contained one USA control, one Kerala control and 24 dosimeters which were distributed among the populace in Kerala for 44 days. The elapsed time between preparation of the dosimeters and readout was 89 days. The results of this experiment were disappointing in that where three aliquots per dosimeter were read, the variance was sometimes as large as ± 30%. This factor, together with incomplete control-dosimeter information and a large total elapsed time, prevented useful analysis of the data. However, the highest indicated exposure rates were 10 to 20 times the environmental background levels of the U.S.

A second set of dosimeters was assembled and sent to Kerala. Instead of single containers of LiF, these units were heat-sealed plastic packets, each of which contained two sealed polyethylene tubes of LiF powder and one sealed LiF single crystal. One tubular dosimeter in each packet was purchased from a commercial source and the other was an equivalent provided by the X-Ray Exposure Control Laboratory (XECL); the single-crystal dosimeters were provided by the Technical Operations Branch, Rockville.

Fifty of these tri-packs were used in the second experiment; four were retained in the USA as controls, four were immediately returned upon their arrival in Trivandrum to account for shipment background variations, and four were retained in Trivandrum as controls near the distribution area. The remaining 38 tri-packs were distributed among the populace in Kerala. All controls were kept in unshielded locations. Because of difficulties encountered in the distribution of the dosimeters, the population background exposure time for each packet varied from 34 to 40 days. The units were then collected and returned to the Research Branch Laboratory together with the Trivandrum controls.

Dosimeters were returned to their source of preparation for readout and calibration. The raw readout values and calibration data were used by the Radiation Physics Unit to calculate the background exposure values. Results are listed in Table 2 by geographical area, occupation, and sex.

The data have been discussed with Dr. M. Alfred Haynes, Agency for International Development, who was in Trivandrum and helped plan the distribution of the dosimeter packets. Although there were large differences between the calibrations of the dosimeters, the capability of this dosimetric method has been proved for the determination of personnel background exposure. However, in a full-scale application, costs could be quite high unless the preparation and analysis of the dosimeters were automated. Before further studies of this nature are undertaken calibration techniques and standards must be established.

TABLE 2. EXPOSURE OF DOSIMETERS BY AREA, OCCUPATION, AND SEX[a]

	No. of Dosimeters	Range (mR/day)	Ave. Exposure (mR/day)
AREA			
Kovilthottam	2	2.34, 3.13	2.73
Neendakara	6	0.500-8.60	2.37
Mekku-Chavara	6	1.07 - 1.96	1.45
Panathura	1	-	1.37
Alappad	10	0.379-2.10	1.20
Vizhinjam	1	-	0.679
Ponmana	2	0.567,0.631	0.599
Poonthura	2	0.293,0.323	0.308
Eravipuram	6	0.152-0.318	0.230
OCCUPATION			
Fishing	8	0.293-8.60	2.46
Plant Worker (Chavara)	6	1.07 - 1.96	1.45
Housewives	11	0.379-2.54	1.16
Agriculture and Misc.	5	0.526-1.15	0.721
Plant Worker (Eravipuram)	6	0.152-0.318	0.230
SEX			
Males	23	0.152-8.60	1.35
Females	13	0.432-2.54	1.12

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a. Rockville background rate - 0.137 mR/day.
Mail background rate - 0.621 mR/day.
Trivandrum background rate- 0.502 mR/day.

3. Radiological Aspects of X-Ray Epilation in the Treatment of Tinea Capitis

Tinea capitis is a benign fungal infection which has occurred in epidemic proportions among prepubescent children. Prior to the introduction of such drugs as griseofulvin, part of the treatment for the disease required the complete, but temporary, epilation of the scalp by superficial X irradiation. Usually a single epilation was sufficient; however, duplicate, and in some cases a third X-ray exposure was required. The Epidemiology Section of the Research Branch is interested in initiating a study of over 12,000 patients treated by this method in Israel. X-ray epilation was thought to incur small risk since it was believed that the skull absorbed most of the incident radiation, and that nervous tissue was radio-resistant. Recent reports indicate that the central nervous system is sensitive to X-ray exposure levels comparable to those used in the treatment for tinea capitis.

The radiological study consists of (i) phantom dosimetry to provide distributions of absorbed dose and secondary photon and electron spectra in the skull, brain, eye, thyroid, and thymus and (ii) an investigation of morphological and physiological changes in laboratory animals irradiated in a manner similar to patient treatments.

a. Phantom Dosimetry

Several investigators have reported phantom dosimetry for tinea capitis; most of this work has focused on determinations of scalp exposure uniformity. None of the reported dosimetry has covered the full range of both X-ray technique and skull development which, according to the comparisons in Table 3, are important to the establishment of typical skull and central nervous system exposures for epidemiological needs.

TABLE 3. PERCENT OF X-RAY ENERGY ABSORBED OR TRANSMITTED BY SKULL

Half-Value Thickness, mm Al	Effective Energy, kev	Absorbed by Bone Thickness, percent[a]		Transmitted by Bone Thickness, percent[a]	
		0.2 cm	1.0 cm	0.2 cm	1.0 cm
0.3	15	88.7	99.9+	11.3	0.002
4.0	40	11.0	43.2	89.0	56.8

a. Values given in fractional percentage.

To provide head phantoms typical of the age distribution common to tineal infections, three children's skulls, ages 3, 6, and 12 years, have been obtained. The heads are being reconstructed by substituting Mix-D (paraffin, pine resin, polyethelene, TiO_2, MgO) for the soft tissues. Mix-D is considered to be a suitable medium since radiography (100 kvcp, HVL = 2.14 mm Al) of the mixture suspended in water has demonstrated its water equivalence. To determine exposure ranges and mock-therapy set-up reproducibility, an Alderson Rando phantom is used. The tissue equivalence and skull size of this phantom are not suitable for all the needs of this study, but it does provide a durable phantom with good dosimeter access and geometric reproducibility.

Primary dosimetry is based upon an NBS calibrated Victoreen r-Meter and ionization chambers. Half-value layers and effective energies are determined with filters of pure copper (electrolytic) and aluminum (99.99% + Al). Since it is technically undesirable to use r-Meter chambers in phantom dosimetry, BG ionization chambers (Machlett-Sievert) with Randometer (modified Minometer) and lithium fluoride radiothermoluminescent dosimeters (CONRAD system) have been tested for possible use.

Thirty-six BG chambers have been tested and grouped according to charge leakage, reproducibility of measurement, and radiation response. The energy dependence of a sampling of these chambers has been found to be greater than expected from the literature. Further calibration is necessary before these dosimeters can be routinely used.

Thermoluminescent dosimetry with LiF powder offers a unique combination of small energy dependence and a very large range of linear response to X rays. To date, the dosimeters used in this study have consisted of LiF powder (TLD-100) in gelatin capsules. For calibration, BG chambers and LiF dosimeters are suspended in air on Mylar tape and exposed to a calibrated horizontal beam of X radiation which has been standardized with the Victoreen r-Meter.

Techniques for measuring medium-energy X-ray spectra are being developed. Spectral data are necessary for determining the relationships between primary and secondary photon spectra and their accompanying electron spectra; dosimeter responses; dosimetric parameters such as absorbed dose, linear energy transfer, local energy density (molecular scale); tissue interface phenomena; and various biological responses.

Detection optimization and spectrometer calibration are being done with radionuclide radiations and fluorescence X rays. The pulse height analyzer system used in this work is a Tullamore SCIPP-1600 with typewriter and punched paper tape readout; the tape code is ompatible with the IBM-1620 computer. Three detectors are being developed: (i) 6 mm x 25 mm NaI(Tl) cleaved crystal, 0.005-inch beryllium window and Amperex XP1110 photomultiplier tube, (ii) 1 inch x 1 inch NaI(Tl) machined crystal, 0.005-inch Be window and RAC 8575 photomultiplier tube, (iii) XeN_2 proportional detector, Be and Al windows, Reuter-Stokes RSG-30A. The 6-mm crystal detector and the proportional counter are used to measure radiations below 100 kev. The 1-inch crystal detector permits spectra to be measured up to 250 kev without necessitating unusual data corrections.

b. Effects of Tineal X Irradiation on the Central Nervous System

An effort is being made to determine indications of selected chemical and morphological changes in brain which may result from exposures such as those incurred during tineal X-ray epilation. At this time the methods development phase of this study consists of chemical and morphological investigations using beagles.

The chemical study consists of analysis for dose-induced changes in the fatty acids of brain tissue, and cation, anion, and protein concentrations in the cerebrospinal fluid. Of particular interest are the concentrations of Na^+, K^+, and chlorides.

The brains of sacrificed animals are fixed in glutaraldehyde and processed by infusing and potting in Cellosolve and Pyroxylin before being cut into serial sections for gross examination. Selections can then be made from the individual sections for blocking and preparation of slides for microscopy.

To determine the dose distribution in the dog brain a phantom was made from a beagle skull (Figure 17). LiF-gelatin dosimeters are located as shown in Figure 18, and exposure is limited to one hemisphere. Preliminary results indicate an exposure to the unirradiated hemisphere equal to 20% of the irradiated hemisphere. Dosimetry of this type is needed to establish fully the accuracy and precision of the dog brain exposure and to assess the feasibility of using single hemispherical irradiations in a biological experiment.

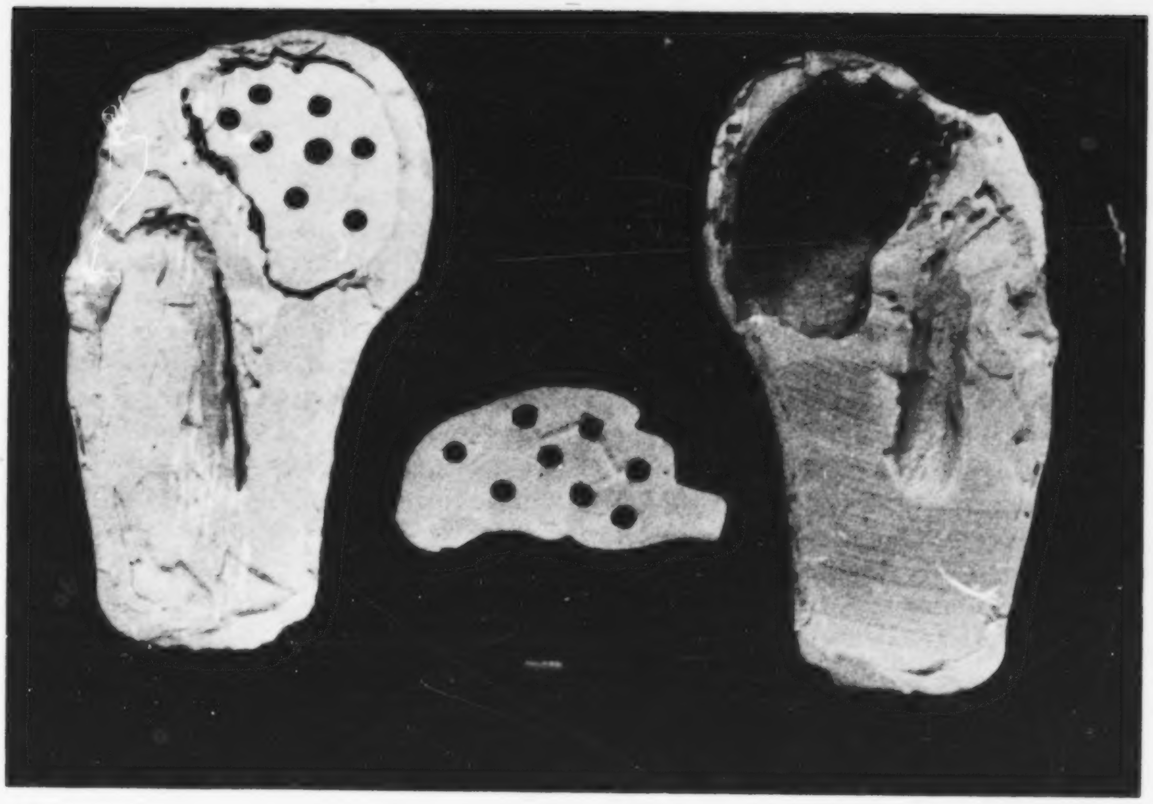


Figure 17. Phantom Dog Head Showing Phantom Brain and LiF Dosimeter Locations.

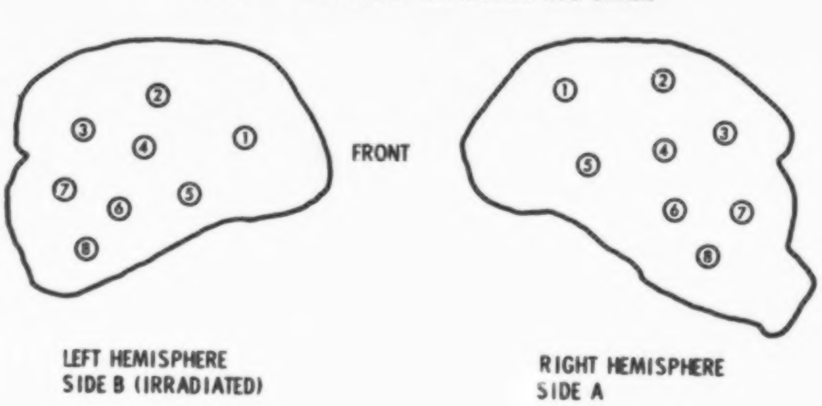

DOSIMETER LOCATIONS IN PHANTOM DOG BRAIN
②
③
④
①
⑦
⑥
⑤
⑧
FRONT
①
②
③
⑤
④
⑥
⑦
⑧
LEFT HEMISPHERE SIDE B (IRRADIATED)
RIGHT HEMISPHERE SIDE A

Figure 18. Dosimeter Locations in Both Hemispheres of Phantom Dog Brain.

D. RADIATION ONCOLOGY AND PATHOLOGY

N. C. Telles, L. Nelson, E. P. Mishkin

The principal objective of this research is to investigate the pathogenetic mechanisms which underlie tumorigenesis following radiation. The ultimate goal is to meaningfully relate these mechanisms to observations of tumorigenesis in humans. The current approaches of the program to the problems of radiation tumorigenesis include light and electron microscopy and enzyme induction methods. In addition, transplantation studies, cell transformation studies, studies in altered immune responses, chemical and viral influences in radiation tumorigenesis, and age sensitivity of the thyroid gland are all being considered for investigation.

In the current oncology program radiation co-carcinogenesis studies are receiving considerable emphasis. It is well known that in a number of instances malignancy induced by radiation can be enhanced or otherwise altered by manipulating one or several of the experimental parameters. For example, partial body shielding of the spleen or ovary may reduce or completely prevent the appearance of lymphoma or ovarian tumors in mice. Partial or complete ablation of the thyroid may result in pituitary tumors in mice but this can be prevented by giving thyroid hormone. Likewise, overstimulation by the pituitary may result in increased numbers of thyroid tumors and the number of such tumors is increased if the thyroid gland has previously been irradiated.

Of special interest are studies with mice that have been thymectomized before receiving whole-body irradiation. The lymphoma incidence in thymectomized mice is not unusual. However, following transplantation of isologously derived thymus glands, these mice promptly develop thymic lymphoma much as if the thymus graft were serving as a co-carcinogen.

Another study of similar interest involves radiation and urethane as co-carcinogens in mice. The order of administration of these two agents markedly influences the induction of leukemia in the treated mice. Thus, if urethane is administered first and then the radiation is given, very little occurs. However, if the animals are first radiated and then the urethane is administered a high incidence of leukemia is observed.

The above studies suggest that several factors must co-exist in treated animals before certain kinds of tumors can be induced by radiation. Furthermore, even the order of administration of co-carcinogenic agents may be of importance.

In our current studies radiation and ethionine are being investigated as possible co-carcinogens. Ethionine has long been known as a liver toxin and more recently as a liver carcinogen. Radiation has only infrequently been implicated as producing liver tumors. These agents are being used in an effort to establish whether co-carcinogenicity will occur.

1. Radiation-Ethionine Co-Carcinogenesis Study

This study is designed to establish whether radiation plus ethionine produce more liver tumors in rats than either radiation or ethionine alone. In the initial phase of the study a single radiation dose was used and the animals were given radiation to the liver area or to the whole body. Four levels of ethionine were incorporated in a special diet.

The toxicity of ethionine is illustrated in Figure 19, which shows normal liver and various degrees of fatty metamorphosis in the parenchymal cells of rats fed different ethionine diets. Bile duct hyperplasia was another finding noted in the ethionine-treated animals. Radiation changes were also prominent two or three days after exposure. No animals were lost from acute radiation effects.

To date, of 303 rats entered in the study, 22 have died with mammary tumors present and 2 have had fibromas (Figure 20). Thirty-nine other rats have developed mammary tumors and are still living. No hepatomas have yet been observed in this study. Tentatively the study will be terminated at the 18th month with the sacrifice of all remaining living animals.

2. Effect of Testosterone on Ethionine Inhibition of Hydrocortisone-Stimulated Tryptophan Pyrrolase in Liver

Ethionine is known to have several effects on cell metabolism. Prominent among these is its effect on non-specific enzyme induction by hydrocortisone as well as its effect in inhibiting protein synthesis. Both these effects are probably related to the fact that ethionine tends to deplete the cell of free or available adenosine triphosphate.

Other investigations have established that (i) ethionine is relatively more toxic for female rats than for males, (ii) the basal levels of the liver enzyme tryptophan pyrrolase (TP) are higher for male rats than for female rats.

Experimental results thus far indicate ethionine inhibits the induction of TP by hydrocortisone as much as 70%, and that male Osborne-Mendel rats are affected to the same extent as females. It also appears that in addition to inhibiting TP induction, ethionine displaces the induction peak so that it is delayed by as much as 2 hours, the normal induction peak occurring at 5-6 hours.

Results also clearly indicate that testosterone raises the level of total induced enzyme without significantly changing the peak

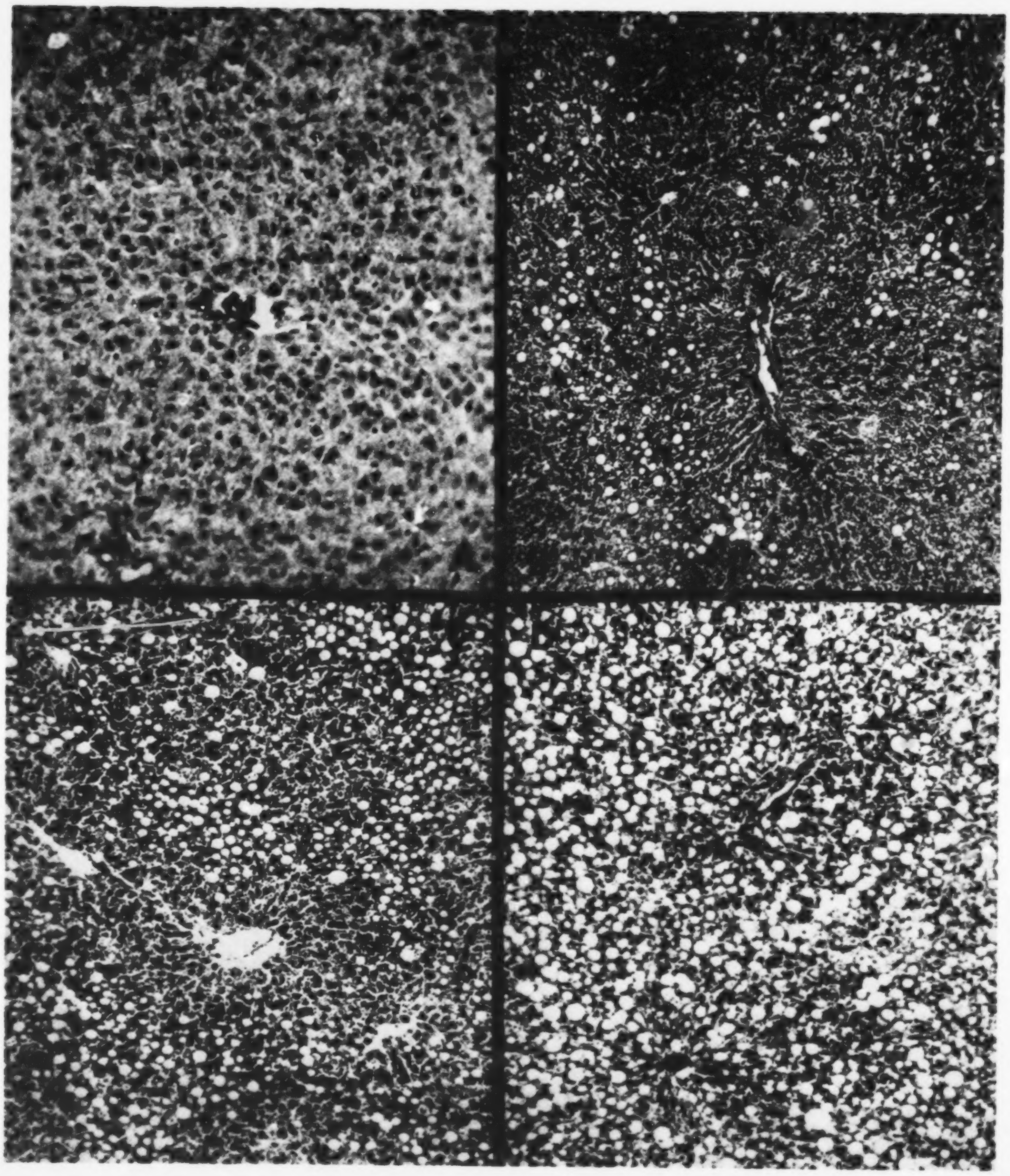


Figure 19. Photomicrographs of Livers of Rats in Ethionine-Radiation Experiments.
A) Liver from untreated rat. X125
B) Slight fatty metamorphosis. X75
C) Moderate fatty metamorphosis. X110
D) Extensive fatty metamorphosis. X110

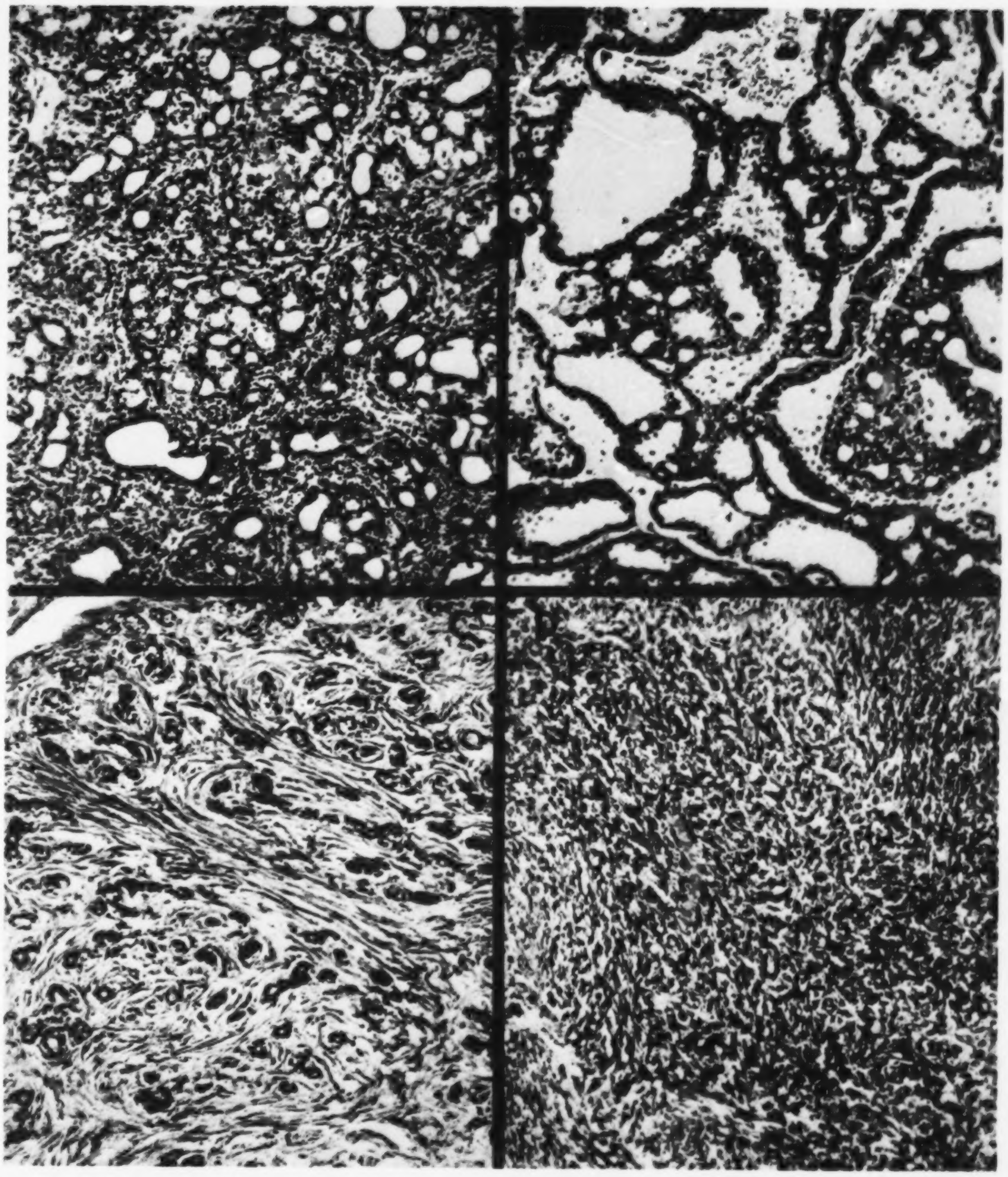


Figure 20. Tumors from Ethionine-Radiation Experiment.
A) Primarily glandular, epithelial mammary tumor. X75
B) Papillary cystadenoma of mammary gland. X125
C) Primarily fibrous mammary adenoma. X110
D) Fibroma. X110

induction time. In addition, it appears from preliminary studies that testosterone has no significant effect in reversing the enzyme inhibition produced by ethionine. A similar study using irradiated animals is in progress.

3. Ultrastructure Studies

Studies at the ultrastructure level are being conducted on the pathogenesis of specifically induced tumors. These studies are part of the radiation-ethionine co-carcinogenesis investigations. They include an evaluation of the long-term changes in radiated liver tissue, and include ethionine-treated liver as well as radiation-ethionine-treated liver. In all these studies, electron microscopic observations are being correlated with light microscopic findings.

When fed at proper doses for several months, ethionine will induce hepatomas in rats. In addition, ethionine also has acute toxic effects which are apparent by means of both light and electron microscopy within a matter of a few hours.

In these studies, female Osborne-Mendel rats were injected intraperitoneally with ethionine at doses of 1 mg per gram of body weight. Animals were sacrificed at 1/2, 3, 5, and 24 hours. Stained sections showed increased fat deposits in the parenchymal cells as early as 1/2 hour after ethionine injection. At 24 hours postinjection marked fatty deposits in the parenchymal cells were present.

Ultrastructure examination of the same livers revealed the fat deposits (Figure 21), but in addition there was an apparent disaggregation and dispersal of the polyribosomal aggregates normally present in the cell (Figure 22).

The final results will be compared to parallel evaluations on livers obtained from rats fed ethionine over many months. The possible relationship between morphological changes and the development of hepatomas will be studied.

4. Pathology Support and Other Services

A histopathology laboratory is being operated under the supervision of a veterinary pathologist. Routine as well as special preparative and staining techniques are used. Electron microscopy is performed with a Siemens 1A electron microscope. In addition to studies of tumorigenesis, support is provided to other program areas within the Research Branch Laboratory.

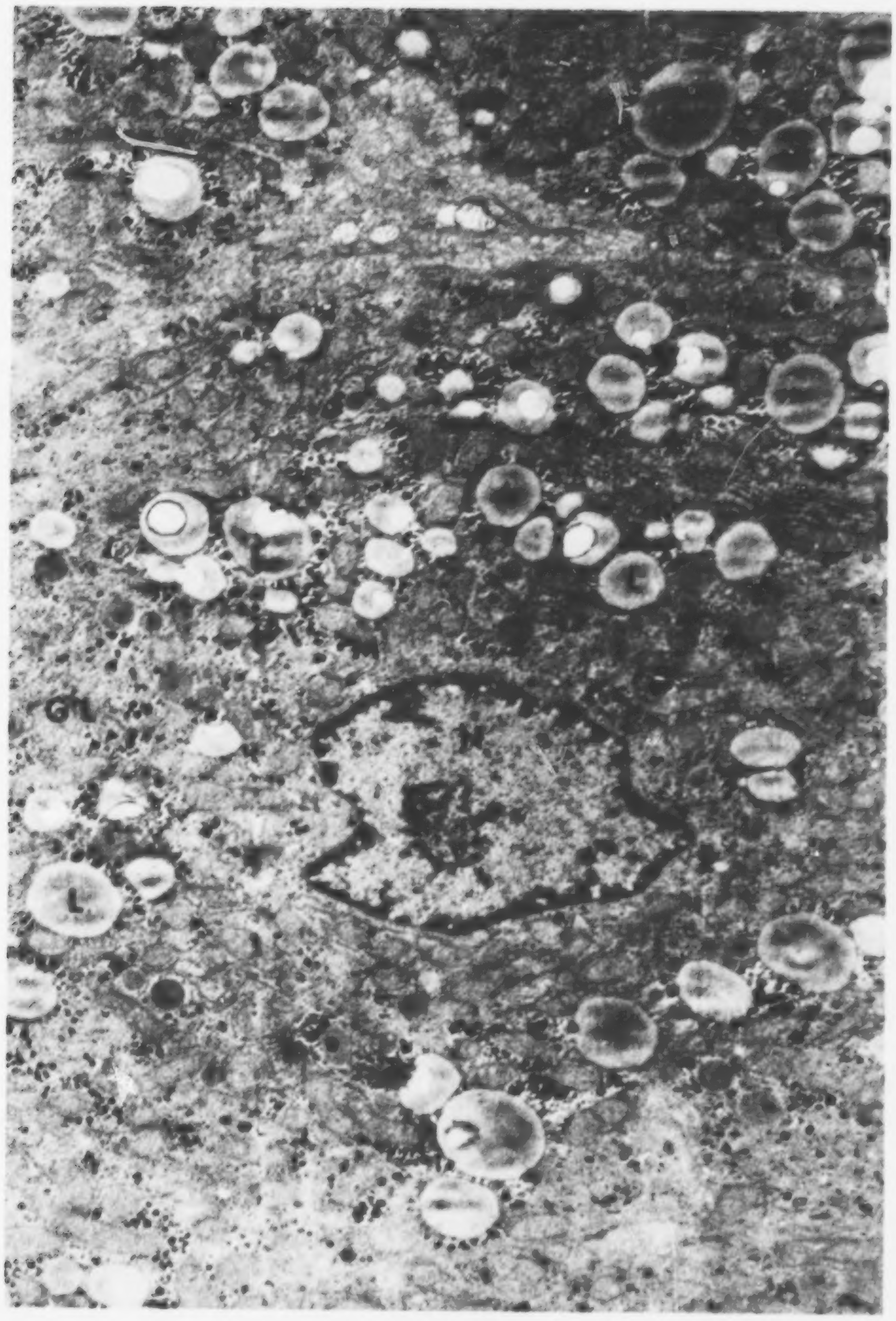


Figure 21. Hepatic Parenchymal Cell, X7,900. Animal sacrificed 24 hours after injection with ethionine (1 mg/g body weight, intraperitoneal). There is an increased number of lipid droplets (L) in the cell, located at the cell periphery. The cell nucleus (N), mitochondria (M), glycogen droplets (GL) and endoplasmic reticulum do not appear unusual at this magnification.

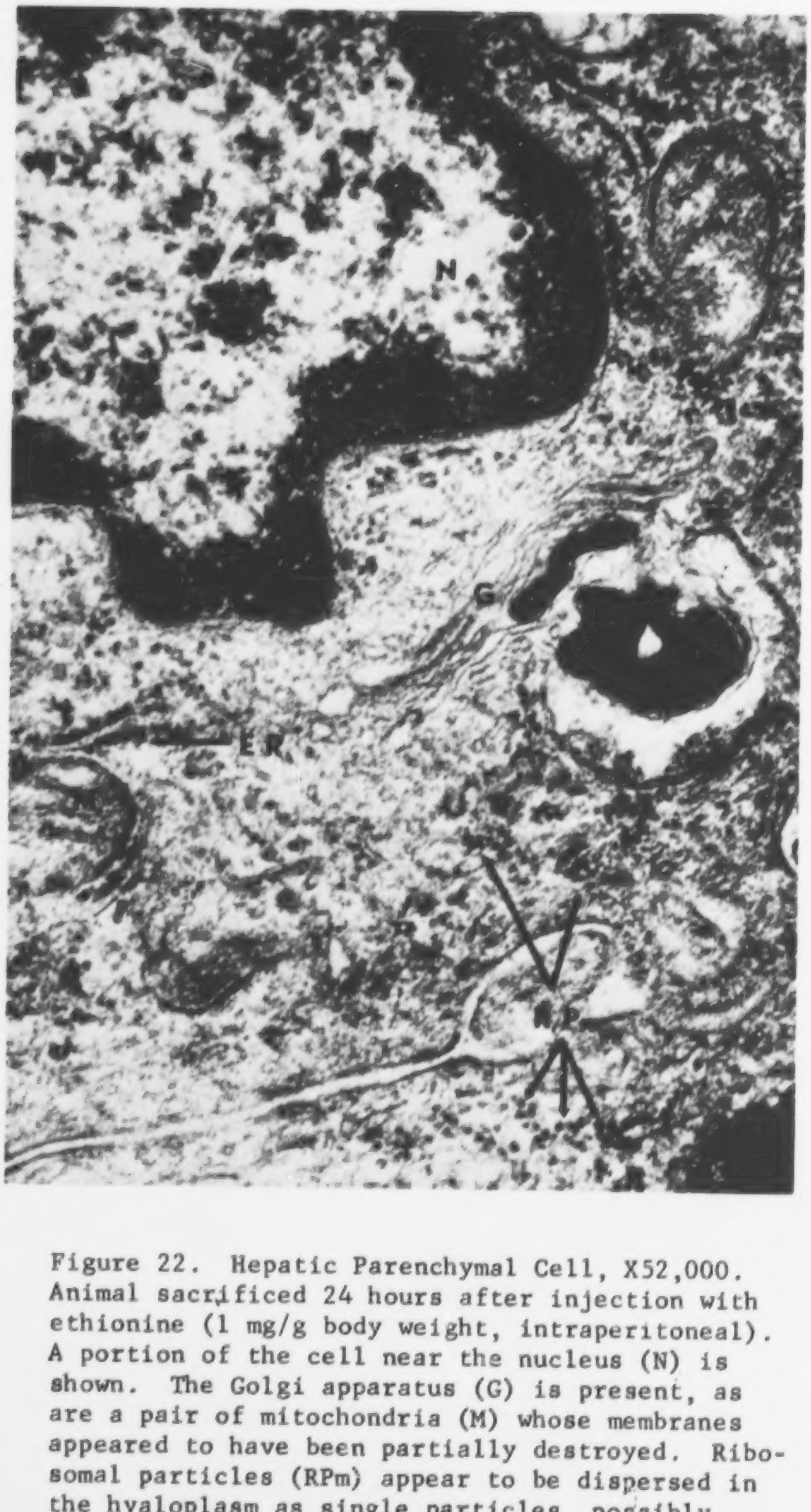


Figure 22. Hepatic Parenchymal Cell, X52,000. Animal sacrificed 24 hours after injection with ethionine (1 mg/g body weight, intraperitoneal). A portion of the cell near the nucleus (N) is shown. The Golgi apparatus (G) is present, as are a pair of mitochondria (M) whose membranes appeared to have been partially destroyed. Ribosomal particles (RPm) appear to be dispersed in the hyaloplasm as single particles, possibly arising from the endoplasmic reticulum (ER).

E. COLLABORATIVE RADIOLOGICAL HEALTH LABORATORY

DRH Project Officer, A. K. Davis
CSU Project Director, R. J. Garner

The Division of Radiological Health has as one of its main goals the determination of the long-term effects of low doses of ionizing radiation. A great deal of this work is carried out through Research Branch contracts with Colorado State University and with additional funds from the National Institutes of Health. The primary objective of the Collaborative Radiological Health Laboratory (CRHL) at Colorado State is to examine and characterize the long-term effects following exposure of dogs to a single whole-body dose of radiation during embryonic, infantile, or adult life. By using the effect of exposure as an indicator of sensitivity to radiation, the relative radiosensitivity at various ages can be determined. The long-term experiment designed to achieve this objective has been formulated in outline but before detailed protocols can be set down a number of preliminary studies are indicated. These have occupied the greater part of the effort over the past few years.

Reorganization of the project during the past year has proved to be very beneficial. In May 1965 the project was assigned a full-time director; in June, the Pathology Section was activated and now processes all the pathological and histological specimens arising from current investigations. The addition of a second senior psychologist has greatly enlarged the capabilities of the Psychology Section. A further development has been the initiation of studies within the Clinical Pathology Section which belong to the area of biochemistry rather than that of clinical pathology.

1. Radiosensitivity of the Beagle at Various Ages

W. J. Tietz

A range-finding experiment has been initiated (i) to determine the relative sensitivity of beagle dogs exposed to radiation at 8, 28, and 57 days postconception, and at 2 days, 10 weeks, and 1 year of age using the median lethal dose (LD_{50}) as the criterion of sensitivity; and (ii) to estimate the theoretical LD_5 of exposed dogs at these ages. Four exposure levels at each age were chosen initially to bracket the LD_{50}. As results have accumulated these exposures have been modified where necessary.

Pregnant bitches are exposed bilaterally to a 400 Ci cobalt-60 source with all but their abdominal regions shielded; pups and adult dogs receive bilateral whole-body exposure. The exposure rate 1 meter from this source is approximately 5 R/minute. The criterion employed is survival to 30 days after birth in the case of pups irradiated *in utero* and to 30 days after exposure in those animals irradiated postnatally. The best estimate of the LD_{50} for 2-day-old pups (the only age for which enough data are available) is 573 rad (547 to 611 rad within 5% confidence limits) and of the LD_5, 477 rad.

2. Biometry and Statistics

G. A. Angleton

The special facilities of the Biometry and Statistics Section handle the vast amount of data accumulated through the experiments at CRHL. The primary scope of work during the past year has been directed toward (i) systems development for data acquisition, (ii) scientific programming, (iii) data processing, (iv) documentation, and (v) consultation.

The data acquisition system utilizes an optical reader that is completely functional. Investigators record experimental data directly on special sheets that this device can read automatically. In the near future it is anticipated that all of the routine data processing can be performed on demand with an expected turn-around time of less than 24 hours after new data and requests are given to the Biometry Section.

Work is continuing in the area of genetic and pedigree analysis. A program for frequency analysis on litter size and the distribution of sexes is completed.

3. Pathology

R. D. Phemister, J. N. Shively

a. Beagle Colony

Necropsy examinations prior to June 1965 were limited to isolated deaths of special importance. Since establishing a pathology service within the laboratory, every mortality in the colony is investigated and results are recorded systematically. A program of consecutively necropsying all dead animals in the cesarean derived, barrier-maintained (CDBM) colony has been initiated (Figure 23).

In each case the primary cause of death and any major contributing causes are sought. Gross abnormalities are confirmed histopathologically whenever appropriate. In the absence of gross lesions, results of microscopic examinations of major organ systems provide positive diagnoses.

Puppy mortality occurs primarily in groups younger than weaning age. In these younger animals necropsy is generally confined to gross inspection. Although only one anomaly is entered in the table, several, mostly minor malformations are recorded as secondary diagnoses.

Figure 23. Puppies That Will be Part of the Barrier-Maintained Colony are Delivered by Cesarean Birth Within This Sterile Cabinet.

b. Range-Finding Experiment

Since December 1965 when the range-finding experiment began (see p. 41) the Pathology Section has collected brain, optic nerve, kidney, and eye tissue for intensive morphologic study. The Pathology and Ultrastructure Sections have cooperated closely so that gross, microscopic, and ultrastructural examinations can be interrelated. A light and electron microscopic study of the lungs of a subgroup of these animals is being carried out as a doctoral research project by a graduate student in the Department of Anatomy.

c. Pilot Experiment

Animals that die in the pilot experiment (see p. 45) are received by the Pathology Section fixed in formalin. Brains are removed and fixed separately. Developmental malformations in these animals are currently being evaluated. Twelve survivors of the pilot study have been sacrificed for more detailed morphologic study of brain, eye, and kidney.

d. Pathology Research

The initial research efforts of this section were concerned with the methods for studying cell differentiation and migration and myelination in the brain, and developmental and degenerative processes in the kidney and eye. Normal development of these organs was surveyed as a prerequisite to selecting ages and sites for intensive investigation. In addition, alternate ways of handling and processing specimens and numerous special staining procedures were compared.

To insure that the light and electron microscopic studies most effectively complement each other, two aldehyde fixatives--glutaraldehyde, which has found increasing favor in electron microscopy, and formaldehyde, which is a standard for conventional histology--have been compared. As a result of this work, glutaraldehyde has been adopted for eye fixation and is still being investigated for brain. Formaldehyde remains the fixative of choice for tissues examined by conventional histopathology.

4. Effects of Irradiation During Implantation on Survival of the Beagle Embryo (Pilot Experiment)

W. J. Tietz

Irradiating female rodents after fertilization but before implantation causes high and rapid mortality of the fertilized ovum. Survivors generally are free of obvious defects, exhibit normal fertility, and show no evidence of decreased survival throughout life. Irradiation during the period of early organogenesis, on the other hand, produces central nervous system (CNS) and other abnormalities; other characteristic effects of irradiation during this period are high neonatal mortality, and decreased birth weight and growth rate.

In the dog, in contrast to the rodent, the neural folds develop as the embryo begins localization in the uterine horn (at about 16 days after breeding) and hence before invasive implantation. The dog presents a situation in which initiation of differentiation of the blastocyst apparently occurs before physical implantation. This offers an opportunity for determining whether the change in the type of response to irradiation seen in the rodent embryo at implantation is related to the stage of differentiation or to the degree of dependence on the maternal tissues.

This experiment examines the stage of development of the beagle embryo when the characteristic response to irradiation changes from prenatal to neonatal mortality. Results will provide information for selecting an age, very early in organogenesis, when irradiation of the embryo would be expected to profoundly affect the CNS, but would not deplete, to a significant extent, the number of animals born alive.

Twenty-three females had been entered into the experiment as of June 1, 1966 (Table 4). Three of these dogs failed to produce puppies. Of the remaining 20 litters, 17 were from dogs bilaterally X irradiated with a dose of 100 R, on the 13th, 16th, 19th, 22nd, or 25th day after breeding; three litters were controls.

TABLE 4. MORTALITY OF LITTERS BORN AFTER IN UTERO IRRADIATION

Irradiation Time[a]	Bitches Bred	Litters Born	Pups Born	Estimated Loss In Utero[b]	Neonatal Mortality[c]
13	5	5	28	10	54
16	4	3	11	60	82
19	4	2	5	80	60
22	3	3	19	Nil	100
25	4	4	23	10	48
Controls	3	3	19	-	21

a. Days after breeding when dam was irradiated.
b. Percent deficit from controls.
c. Percent of pups born that died within 10 days.

The *in utero* death rate is near maximum at 19 days, but the maximum postnatal effect appears not to occur until irradiation at the 22nd day after breeding. Of those litters irradiated on day 22, none of 19 puppies born survived 10 days. The increase in neonatal mortality suggests that little selectivity for postnatal survival is being exerted by *in utero* irradiation. If the *in utero* survivors were the more vigorous animals, it would be expected that postnatal mortality would decline as *in utero* mortality (judged by decline in litter size) increases. A more definitive analysis of the data will be conducted at the conclusion of the experiment.

5. Experimental Psychology

J. A. Modrick

Major facilities have been designed and constructed for psychological research during the past year by modifying unfinished space in the CRHL building. Four research areas have been established: Delayed response, discrimination learning, maze learning, and avoidance conditioning. These areas have been chosen because they represent behaviors that may be sensitive to biological insult. Initial work has been done to develop procedures and evaluate the apparatus, and specific research studies are currently being designed. Presently only nonirradiated animals are being used to provide control data.

During the year, the Psychology Section proposed working with 8- to 12-week-old animals to reduce the number of dogs rejected as subjects. Animals that adapt to handling, apparatus, and experimental procedures at this age appear to be easily socialized and tractable, and can learn and perform more readily than animals entered into studies for the first time at ages of 9 to 12 months. The rejection rate for the younger subjects is less than one in six, in contrast to the rate of one in four or higher for the older dogs.

6. Clinical Pathology

a. Blood Studies

M. M. Benjamin

The Clinical Pathology Section at CRHL conducts extensive blood analyses of beagle dogs. Both the hematology and blood chemistry of samples taken from the animals are analyzed and recorded. These data aid in determining the mechanisms by which ionizing radiation affects the animal.

b. Enzyme Studies

M. T. Wagner

As part of the program to determine the effects of *in utero* radiation on selected enzyme systems in the dog, preliminary studies are being made on glucose-6-phosphatase activity in the liver and kidney. Although enzyme systems in various mammalian species have been exhaustively studied, the literature reveals very little work in the dog. Further, the application of *in utero* irradiation in the canine is nonexistent. For this reason the problem requires not only the determination of radiation dose-time effects, but a firm establishment of a time-effect value for controls.

The livers and kidneys of approximately 80 animals have been studied using various combinations of exposure dose, age at irradiation, and age at sacrifice. A clear pattern is not yet available because of the limited number of animals studied. There is, however, a very good indication that, for this particular enzyme system, the activity at various ages in the beagle liver does not compare with other mammalian species previously studied.

c. Fetal Hemoglobin

R. J. Garner, M. T. Wagner

Further work to detect radiation by measurement of enzyme on protein products is being performed on red blood cells. Recent efforts to detect fetal hemoglobin in 1-day- to 2-year-old dogs by agar gel electrophoresis revealed no detectable fetal hemoglobin or other significant changes in the hemoglobin pattern. Two other testing procedures for differentiation of adult and fetal hemoglobin have now been included, in addition to the electrophoresis. One is an alkali denaturation chemical method, and the other is an acid elution hemoglobin concentration analysis.

Blood from fetuses 57 and 63 days in gestation, from young dogs less than one year old, and from adult dogs were examined by each of the three procedures. No differences appeared at any of these ages to indicate the presence of fetal hemoglobin. Blood from fetuses younger than 57 days will be tested for fetal hemoglobin as soon as it is available. These and chromatographic results will be necessary before a conclusion can be made concerning the presence of detectable fetal hemoglobin in the dog.

7. Physiology

W. J. Tietz

The Physiology Section during the year studied (i) the influence of cold immersion on the development of thermoregulation, (ii) the characterization of the neonatal puppy reflexes and their modification with age, (iii) the postnatal morphological and physiological development of the canine brain with particular emphasis on the visual system, (iv) development of electronic methods for measuring blood flow, and (v) the most radio-susceptible periods in the development of the embryo (pilot experiment, p. 44).

a. Cold-Immersion Studies

The mechanisms by which mammals regulate their body temperature involve the integrated activity of several elements including (i) calorigenic enzyme systems, (ii) sensory mechanisms, both peripheral and central, (iii) central integrative areas, i.e., hypothalamus and cerebellum as well as brain stem and cord tracts and "centers", and (iv) peripheral motor elements both autonomic (vasomotor) and somatic (shivering) plus their neuro-effector terminals.

Any of these elements could be damaged by in utero irradiation and the cerebellum, for example, is known to be. Although not yet quantitated, it is known that at birth the canine cerebellum, myoneural junction, and hypothalamus are relatively immature. It might be considered, therefore, that these areas would have a lower effective threshold to damaging effects of perinatal irradiation than more mature tissues.

Preliminary studies indicate that subtotal periodic immersion of puppies from birth to the arbitrary age of 10 weeks in a 40° F water bath is a stress that will test the integrity of the homothermic mechanism. Current efforts have been devoted to analyzing the calorigenic activity as it relates to motor function, both voluntary (escape and crying) and involuntary (shivering). Core body temperature, and the weight of the animal can be used to calculate rate of heat loss as the puppies cool during immersion. The alteration of the slope of the cooling curve by somatic motor activity provides information regarding the maximum heat output possible at a given age.

Ninety-five puppies born during the year were used to determine the effect of cold immersion and radiation on the growth rate during the first ten weeks of life. Growth rates of the non-irradiated puppies were very similar in spite of the various immersion treatments. Bilateral in utero irradiation with doses of 4, 16, or 64 R at 4, 14, 18, and 28 days post coitus, caused a marked decline in growth rates. Those puppies that were irradiated and immersed frequently gained at the rate of 31 grams per day, whereas those that were only occasionally immersed gained 26 grams per day. The two groups of irradiated dogs gained in almost identical fashion until about 40 days of age. The discrepancy developed between the 40th and 49th days. The final weights differed by 268 grams per dog with the occasionally immersed group being the lighter.

Growth of the irradiated puppies paralleled that of the other dogs until about the 15th day. Then a definite decline in rate of gain was noted. The slower growth rate persisted through the remainder of the observation period.

Growth rates of in utero irradiated puppies appear to lag behind those of nonirradiated puppies after the age of 15 days. At 15 days the essential elements of the dog's homothermic mechanisms are just beginning to form. A decrease in the growth of the other groups also occurs at this time, but within 5 days--at about 20 days of age--a very rapid growth rate begins. It seems that the second rapid growth period fails to develop in the irradiated puppies.

b. Visual Cortex Investigation

The electrical activities evoked in the visual cortex of normal beagles are being studied with the intent of establishing normal evoked potential patterns following visual stimulation. Such studies are integral in the interpretation of the radiation-induced structural defects observed microscopically.

A system involving a photostimulator and synchronized camera records single responses. In addition, repeated responses are recorded on magnetic tape and, using a suitable converter system, are replayed through an impulse-averaging circuit on loan from General Rose Hospital, Denver. Initial results indicate that the system is operational for single acute experiments.

c. Cerebellum

Investigations into the electrophysiological correlates of cerebellar dysplasia have been initiated in normal anesthetized puppies using electrodes implanted in the cerebellum. Eventually, after normal electrical patterns have been established, the studies will be extended to the use of surface electrodes first on normal puppies and, subsequently, on irradiated puppies from the pilot or range-finding experiments.

d. Pulse Wave Transmission

Changes in vascular wall components are a reflection of aging changes; hence, pulse wave transmission studies and intracardial transmission time may be indicators of radiation-induced accelerated aging. Using pressure transducers, intravascular catheters, impedance devices, and using the R wave of the EKG as a zero time signal, the rate of transmission of physiological disturbance from R wave to appearance of the pulse in the aorta has been determined for one-year-old dogs. The transmission time has been found to be about 0.012 second. Similar transmission time "constants" are being determined for older dogs and for neonatal and adolescent dogs. Pulse wave transmission rates have been obtained for the various regions in the aorta of young adult dogs. Similar determinations will be made for neonatal, adolescent, and aged dogs, with and without radiation exposure.

e. Reflex Development

Somatic reflexes are being tested on puppies that have been entered in the pilot and the range-finding experiments. Fifty-two puppies from 14 litters in the range-finding experiment have been examined. Irradiation times are 8, 28, and 57 days after breeding and 2 days after birth; radiation exposure varies from 45 to 570R. Forty puppies from 18 litters in the pilot experiment that received 100 R at 13 to 25 days after conception have also been tested. The performance of the experimental dogs is being compared with the performance of 24 control puppies from 6 litters.

f. Embryo Timing

Tables using the first day of estrus as the zero day for timing embryo development have such a degree of developmental latitude that they are virtually worthless for the CRHL project. However, if the last day of estrus is used as the zero time and with a breeding period of 24 hours it appears that the variability in developmental timing can be considerably reduced. Efforts to confine the developmental time table to narrower limits are continuing.

8. Ultrastructure

J. N. Shively

a. The Retina of Irradiated Dogs

Glutaraldehyde- or osmium-fixed eyes from dogs receiving low doses of X or gamma radiation are studied by light and electron microscopy. Retinas, collected from about 150 dogs, have been photomicrographed and studied in detail. A marked dysplasia is seen in perinatally irradiated dogs. The magnitude is dose dependent and the effect occurs at dose rates of both 25 R/min (X-radiation) and 5 R/min (γ-radiation). At the lower dose, sampling problems inherent in fine structure studies become paramount. Hypocellularity of the inner nuclear layer has, however, been observed. At least some of the damage appears irreparable since the dysplasia remains apparent at least several months after irradiation. Dogs irradiated after maturation of the retina have evidence of only occasional necrotic cells.

b. Thyroid Glands in Young Dogs

Thyroid glands from 53-day-old beagles, which had been stimulated with 10 units of thyroid stimulating hormone (TSH) at various times prior to tissue collection, are being studied. The material is fixed with osmium tetroxide or with glutaraldehyde for light and electron microscopic studies. Incomplete studies suggest that the thyroid of the young dog responds to TSH stimulation in a manner similar to that reported for rodents. Details of the ultrastructure changes and of the temporal response are being completed.

In other studies, the incidence of thyroid carcinoma in irradiated young animals is investigated. Beagles 53 days old are exposed to total-body X radiation at a rate of 25 R per minute for a total exposure of 350 R. At 1, 2, or 7 days after irradiation thyroid glands are surgically removed and prepared for microscopic examination.

Observations of the photomicrographs indicate that the alterations in the follicular epithelium are most likely due to increased pituitary activity following stimulation by X irradiation. The capillary changes may well be an effect of irradiation and are consistent with the increased capillary fragility and hemorrhagic syndrome that would have undoubtedly developed a few days later if these dogs had been allowed to progress.

F. RADIONUCLIDE METABOLISM PROGRAM

The kinetics of radionuclide metabolism are not clear and require extensive study especially during periods of embryonic development and growth. During these periods of life a relatively small number of body cells may retain a greater proportion of ingested radioactive ions than later in life. Moreover, these young cells may be more radiosensitive than later in life. Kinetic data from animal experiments aid in developing descriptive models of radionuclide movement in the organism, and in revealing its retention and compartmental turnover in tissues. In addition, techniques of autoradiography and microdensitometry help to determine accurate isotopic concentrations per unit of tissue volume, and this in turn improves the accuracy of dose calculations. During embryogenesis and neonatal life, the uptake and retention of environmentally hazardous radionuclides, such as Sr, Cs, and I, are frequently greater than in the adult. The growing tissues also have a lesser ability to discriminate between similar elements, such as Ca and Sr, but their cellular components have a greater radiosensitivity. It is therefore necessary to obtain specific activity values using radiochemical analyses in combination with isotopic concentrations of various body compartments to determine the quantitative differences between young and adult organisms.

1. Strontium Retention in Children

H. N. Wellman

As part of a study to determine the effect of age on strontium-90 retention in children, metabolic balance studies were performed with three 6-year-old and three 9-year-old children. The children were selected as being normal on the basis of clinical history; physical examination; serum calcium, phosphorus, and alkaline phosphatase; routine laboratory tests; and bone-age radiographs. The children were maintained in the metabolic ward of the Cincinnati Children's Hospital for a 15-day balance period and were fed commercially available foods. A balanced diet, recommended by the National Research Council, provided normal intakes of all dietary components. The diet was consumed quantitatively during the balance period and for one month prior to the period. Diet, urine, and feces were analyzed for calcium, phosphorus, stable strontium, and strontium-90 content. Average daily intake, excretion, and retention data showed that children in both age groups retained about 16% of the calcium and phosphorus, and about 6% of the strontium 90 consumed. These studies are being continued to obtain more data at these two ages and also at ages 3, 12, and 15 years.

2. Strontium Metabolism in the Infant and Adult Cat
J. F. Stara, E. R. Berman

a. The Outdoor Feline Colony

An outdoor colony of more than 200 cats has been established for use in radiobiological studies (Figure 24). Because of its prolific and hygienic nature, the feline is well suited both for acute and chronic radionuclide metabolism studies, especially those concerned with placental transfer and turnover in the embryo and the growing offspring. Approximately 100 animals are presently at various stages of a strontium-85, strontium-90 chronic experimental regimen to provide data for dose-effect studies. The remainder of the animals serve for breeding purposes, controls, and for short-term radionuclide ingestion studies.

Advantages of an outdoor cat calony over a similar indoor one include lower cost of facilities and operation, lower mortality from infectious feline respiratory diseases, and greatly increased reproductive efficiency. Growth, litter size, size at weaning, and mortality rates in this colony compare favorably with data reported from the very few cat colonies maintained in England and in this country. Table 5 lists the reproductive rates and indicates that both conception and survival rates are very satisfactory if compared with research colonies utilizing larger mammals.

TABLE 5. REPRODUCTION RATES OF RHRA CAT COLONY

Conception rate, %	93.6	(Based on 52 available dams)
Average litter size	3.5	(1 to 7 kittens)
Stillborn rate, %	7.9	(Based on 176 kittens)
Survival rate, %		
At 7 days postpartum	88.3	(91.4% excluding fostered kittens)
At weaning (50 days)	78.4	(86.3% excluding fostered kittens)
Fostered kittens 7 days old	40	
Fostered kittens 7 to 50 days old	67	

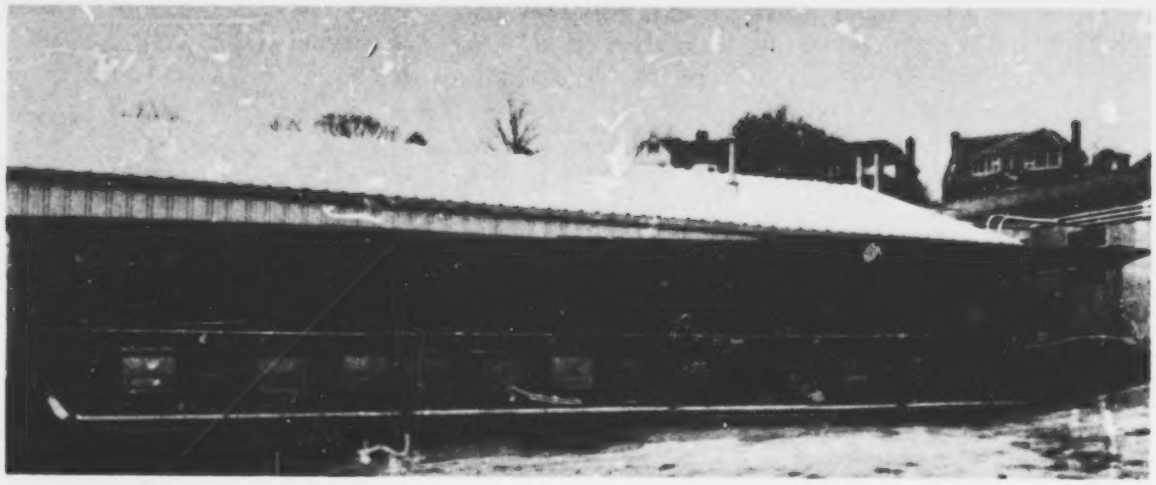


Figure 24. Outdoor Cat Colony at RHRA.

b. Tooth and Bone Analyses

As a part of a feline metabolism study, tooth layers are analyzed and compared with mineral values of bone tissues in an attempt to estimate skeletal burdens of strontium and calcium in cats. Data are recorded on cat "dental charts." Each chart is an accurate anatomical representation of the crowns and roots of normally appearing deciduous and permanent teeth similar to those used for human dental examinations and records.

The schematic drawings are based on the actual size and appearance of the various teeth. This form provides a permanent visual record of the results of dental examinations during the tooth eruption time of each animal. The presence of the individual teeth, both during the life of the animal and during dissection, can be noted on the chart by relatively untrained observers. The observations are being accumulated to be used later for a statistical evaluation of tooth development and eruption time, which may be indirectly used for comparisons with bone tissue.

c. Secretion of Calcium 47 and Strontium 85 in the Saliva of Cats

Strontium and calcium levels in saliva, obtained by pilocarpine reflex stimulation of salivary flow were determined for growing and adult cats. These animals had been labeled by radioactive tracers in one of two distinct modes--single or chronic dose.

In the course of extended stimulation of the glands, two types of saliva are obtained--a serous followed by mucous type. In each case, the mucous type demonstrated a greater concentration of strontium 85 than the serous type. The difference was larger following a single dose than during chronic isotope administration.

In other studies, the strontium-85 and calcium-47 concentrations expressed as percent of initial body burdens in cats were compared. The results indicate that saliva in feline species is a more accurate indicator of the plasma level of both strontium and calcium than the urine.

d. Kinetic Studies

One part of the metabolism program includes a kinetic study in which young cats' skeletons were labeled chronically by feeding the dam a diet with a constant strontium 85, 90/total strontium ratio before and during pregnancy, during lactation, and then feeding similar diets to the offspring. Another group of animals was given a single dose of strontium 85. All animals were measured by whole-body counting during tracer feeding, and for a year following the last dose at ages 0, 1, 2, 4, 6, 8, 12, 16, 24, 32, 48 weeks, and in adulthood. The immense amount of data is being analyzed using a computer program. Some preliminary values demonstrate the different retention patterns in variously aged kittens, and compare animals given a single dose to those chronically labeled.

Assimilation, reduction, and statistical processing of kinetic data, specific activity values, and analysis of strontium and calcium deposition in the embryonic compartment are being carried on at present. Comparison of specific activity of various tooth and bone compartments and the autoradiographic and microradiographic analyses of skeletal tissues and those measurements based on microdensitometry are under way.

3. Effect of Sodium Alginate on the Absorption of Radioactive Strontium and Calcium in Cats

J. F. Stara

A pilot study using 12 animals has confirmed data that show animals fed sodium alginate excrete approximately 50% more radiostrontium than the controls. In another group of younger animals, the difference between alginate-fed animals and the controls was more than 80%.

Kittens given strontium 85 intravenously and fed sodium alginate showed significantly higher excretion of strontium 85 than animals treated similarly but not fed sodium alginate. The strontium-85 body burden of the experimental animals on the 35th day was 25% lower than the controls, indicating that binding of endogenously secreted strontium and alginate occurred in the gut. These animals are being followed for longer times to observe the magnitude of strontium body burden reduction in young kittens. In addition, four groups of cats have been labeled chronically with strontium 85 since conception. Two of these groups are being fed sodium alginate from the time of weaning and the difference in strontium retention among the groups is observed on a long-term basis.

4. Cesium-137 Uptake and Concentration in the Cartilage and Bone of Mammals

J. F. Stara, A. Martin

Attempts to locate radiocesium in bone by autoradiographs indicated that the solutions generally used to prepare specimens for autoradiographic examination removed cesium 137 from bones labeled in vivo.

Bones dissected from rats, guinea pigs, cats, and dogs subjected either to a single dose or to chronic oral uptake of cesium 137, as well as bones from caribou known to have grazed on forage with a high cesium-137 level, were tested. The solvents included water, formalin, alcohol, acetone, ether, chloroform, xylol, benzene and ethylenediamine. Water and formalin dissolved approximately 90 to 100 percent of the radiocesium; the remaining solvents removed 0 to 20 percent (Figure 25). The solubility of cesium bound in bone was determined in animals sacrificed at various times after administration of single and chronic doses of cesium 137. Conditions of chemical solubility and equilibrium were not attained, but the results indicate the losses to be expected in preserving, cleaning, and fixing bone samples.

An attempt was made to measure the radiocesium concentration in bone marrow. Rigorous defatting of bones by benzene extraction removed from 5 to 40 percent of the activity depending on the number of cycles. Extraction with ethylenediamine reduced the cesium content by approximately 50 percent. Qualitative autoradiographs of defatted bones demonstrated that a higher concentration remained in the trabecular regions than in the cortical regions of the bone.

Previous investigations, both in this and other laboratories, have shown that as much as 5 to 7 percent of body cesium is located in bone tissue. The observation that cesium 137 is lost during sample preparation suggests that, in the past, cesium-137 contents in bone may have been underestimated.

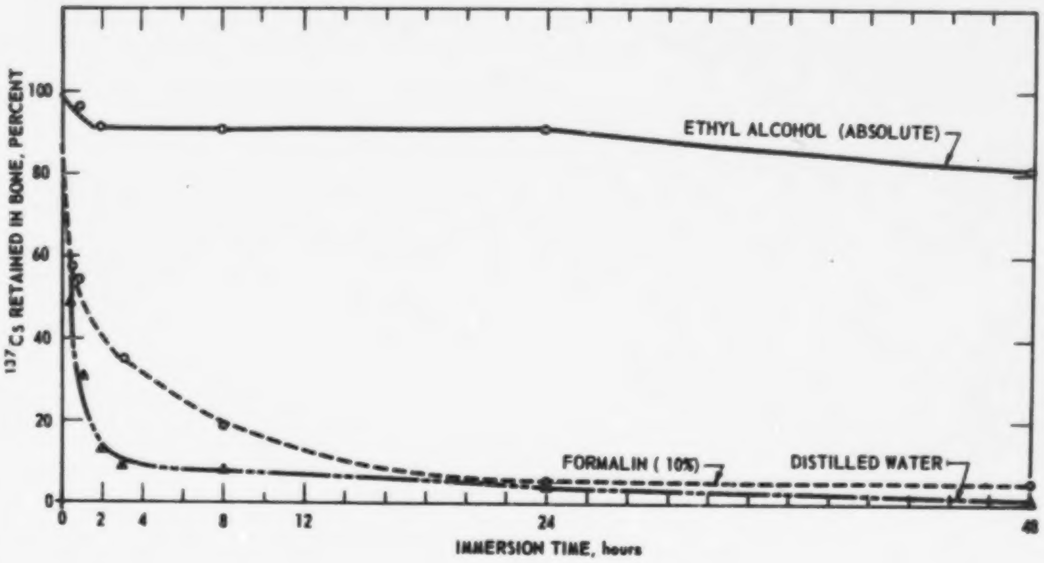


Figure 25. Effect of Selected Solvents
on the Removal of Cesium 137 from Bone.

5. Iodine-131 Distribution in the Embryonic Guinea Pig
J. F. Stara

Autoradiographic techniques have been employed to investigate placental transfer of radioiodine, to determine its localization in embryonic tissues prior to and during organogenesis, and to determine the differential uptake of iodine 131 in primordial stages of thyroid gland development in the guinea pig fetus.

These techniques revealed that the fetal thyroid begins to concentrate iodine 131 at 21 days of gestation. The radioiodine concentration curve at that time shows a sharp rise (Figure 26). Prior to this, several embryonic tissues contain variable but lesser amounts of the isotope. It is possible that the concentration of iodine 131 in the thyroid and other tissues increases with the age and volume of the fetus. This question will be answered when all data are compiled. The analysis of autoradiographic tissue sections indicates that radioiodine in circulating blood is deposited in the most rapidly developing tissues of the embryo. The greatest radioiodine concentration gradient occurs in blood, liver, heart, and nerve tissues.

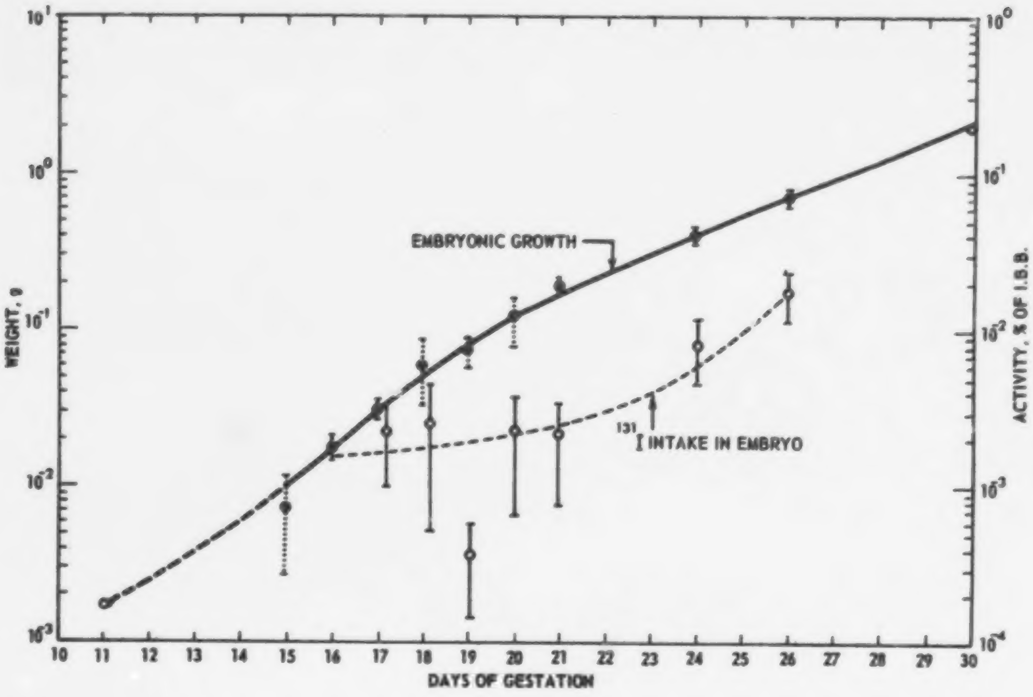


Figure 26. Iodine-131 Uptake in the Fetal Guinea Pig.

The guinea pig placenta has both a maternal and a fetal side. There is evidence, based on radioassay of these organs, that the placenta concentrates iodine on the fetal side, suggesting an active transport mechanism.

To prevent iodine losses from embryonic material and to achieve the best sectioning techniques, various nonaqueous fixatives were tested. Acceptable results were obtained with a formula containing ethanol, glacial acetic acid, chloroform, and mercuric chloride. This method permitted study of iodine 131 distribution in embryonic stages as early as the 10th day of fetal life.

A pilot study using both a surgical- and radioiodine administration-approach to alter the thyroid function of the dam or embryo is in progress. This includes histopathological examination of fetal tissues as well as testing of various physiological functions in the offspring to determine possible teratogenic effects.

6. Histopathologic Changes in Monkeys Exposed to Gamma and Neutron Irradiation

A. K. Davis

Hematological and biochemical changes in the blood of about 75 monkeys irradiated by various combinations of neutrons and gamma photons are being studied at the Yerkes Primate Center, at Emory University, Atlanta, Georgia. Blood from about 30% of the colony has been examined for alkaline phosphatase, acid phosphatase, and nonspecific esterases. Biochemical assays of liver enzymes, electrolytes, creatinine, and uric acid have also been performed. Standard blood values from all animals have been determined routinely. In addition, the bone marrow from 36 monkeys in the atomic weapons exposure (Fitzeau) group has been sampled, and similar samples from 15 animals from other groups have also been taken. Cytogenetic studies of the chromosomes have revealed one animal that apparently has a trisomy of chromosome 21. Pathological examinations are performed on all animals that die. However, a current backlog of work has only recently begun to be reduced with the acquisition of a veterinary pathologist.

Methods to determine kidney function in these monkeys have been perfected, and examination of the glomerular filtration rate, kidney blood flow, the maximum reabsorptive capacity for glucose, the maximum excretory capacity for PAH (para-aminohippuric acid) urine osmolarity, and the concentrating ability of the kidney are under way.

IV. EPIDEMIOLOGY

A. COOPERATIVE THYROTOXICOSIS THERAPY FOLLOW-UP STUDY

E. A. Tompkins

The Cooperative Thyrotoxicosis Therapy Follow-Up Study, initiated in 1961, is an epidemiological investigation designed to determine if deleterious effects are associated with therapeutic doses of radioactive iodine. Specifically, the study tests for an increase of leukemia mortality in irradiated thyrotoxic patients over that in patients treated for thyrotoxicosis by other means. The secondary objective is to determine the incidence of other neoplasia in the exposed and comparison groups. The data will also be used to investigate various questions concerning the disease of thyrotoxicosis and its treatment.

All patients treated for thyrotoxicosis between January 1, 1946 and December 31, 1964, at 30 participating medical centers have been included in the study. Of 36,000 patients, approximately 22,000 were treated with iodine 131. The centers abstract a detailed history of each patient and enroll him in a continuing biennial follow-up program to determine his current health status or cause of death. All data are forwarded to the coordinating center at the Research Branch Laboratory in Rockville where they are prepared for computer analysis. The histories and first status reports on 93% of the patients were received and processed by the end of 1966. Preliminary analysis of dosimetry and clinical data has begun.

The continuing surveillance of this carefully studied population should, in time, enable many possible effects of exposure to radioactive iodine at therapeutic dose levels to be evaluated.

B. EFFECTS OF FETAL IRRADIATION FROM X-RAY PELVIMETRY

E. S. Weiss

The consequences of pelvic X-ray exposures to the offspring of pregnant women have not been definitely established. Diagnostic exposures of the pelvic area are sometimes made before the woman knows she has conceived; at other times exposures may be necessary after pregnancy has definitely been established. In either case, the deleterious effects of such exposures, particularly to the unborn child, should be known.

The study was designed to avoid the liabilities of previous retrospective studies of intrauterine X-ray exposure and to minimize potential sources of bias. An exposed population of about 15,000 was observed during 1964 and was compared with 30,000 matched controls. Although the number of deaths in each cause-race-sex-exposure group was small (0-8), exposure appeared to be associated with higher death rates among white children who had been exposed in utero. However, no appreciable difference between exposed and control negro children was seen.

The number of leukemia deaths (8 as of 1964) was too small to obtain an accurate estimate of the relative risk. For all cancers there appeared to be a threefold risk for whites but no increase in the risk for negroes. Therefore a decision to expand the study population at risk by about 3,000 persons (with 6,000 controls) was made in 1965. In the past year the incorporation of the additional exposed and control individuals has proceeded as planned, and follow-up of the original group has been intensified and extended.

C. TRI-STATE CONGENITAL MALFORMATION STUDY

E. S. Weiss, S. G. Levin

Several years ago, Research Branch negotiated with the University of Minnesota to study the possible association between background radiation levels and the incidence of human congenital malformations. Fifty-three towns with high and low malformation rates were selected in the States of Colorado, Michigan, and Minnesota. Vital statistics were used to rank the towns in Michigan (1958-1959) and Minnesota (1956-1959). Vital statistics for all selected towns in Colorado (1954-1959) were not available so county rates were used in those cases. Birth certificates and hospital records were searched in the selected towns for the same years and comparisons made with the vital statistics data. Generally, the certificate rates showed fewer congenital malformations than the vital statistics rates for the high towns, and showed more malformations than the vital statistics rates for the low towns.

Vital statistics data were obtained for the towns in Michigan for 1960-1964 and in Minnesota for 1960-1963. Malformation rates before 1959 were compared with the rates after 1959. The pre-1959 rates for high towns decreased after 1959, and the rates for pre-1959 low towns tended to increase after 1959. Towns were selected as "priority" towns if they tended to remain high or low in all three series.

Background measurements were made with portable gamma scintillation counters designed at the Cincinnati Radiological Health Research Activities Laboratory and calibrated with a Shonka muscle equivalent ionization chamber. Readings were taken by RHRA teams at intervals of approximately two-tenths of a mile in each town and were converted to µrads/hour. Background gamma radiation levels for towns with high and low malformation rates can be compared using the following tabulation:

BACKGROUND GAMMA RADIATION LEVELS (µrad/hr) FOR SELECTED TOWNS

	Colorado	Michigan	Minnesota
High Malformation Towns[a]	13.04	7.35	8.63
Low Malformation Towns	13.41	7.64	8.38

a. "High" towns are those with more than two malformations per 100 live births.

The observed results are not consistent with a hypothesized relation between malformation rate and background radiation level. A more detailed analysis is being prepared by the contractor.

D. INGESTION AND DOSE MODEL

S. G. Levin

The Biometrics Unit at the Twinbrook Laboratory has initiated a study, consistent with a Division objective of utilizing existing data, to develop a descriptive and predictive mathematical ingestion and dose model.

The first phase of developing this ingestion and dose model consisted of determining the amounts of radionuclides ingested by the U. S. population and examining the relative amounts ingested by segments of the population. In the second phase, doses to specific organs were estimated so that direct comparisons of population groups could be made. Such comparisons may also aid in establishing realistic guidelines for the population and in pointing out the most critical regions or groups. In the third phase of development, actual mathematical models were formulated which can be used to predict population migration and dose based on levels found in food, and to estimate the effect, for instance, of renewed nuclear bomb testing.

A contract awarded to Research Triangle Institute to develop a model for strontium-90 ingestion has been extended to include cesium 137, iodine 131, and strontium 89. The contractor utilized the consumption data on seven foods from the National Dietary Assessment Program (NDAP), and activity level data from the DRH milk network and from the NDAP on a stochastic model to estimate the proportion of persons ingesting fixed amounts of these radionuclides. The estimates are given by region, income, sex, and age. The work on strontium 90 and cesium 137 has been completed. Work on the remaining two nuclides and development of a refined model for infant ingestion are nearly completed.

E. RADIATION EFFECTS ON THE THYROID GLANDS OF INFANTS AND CHILDREN

E. S. Weiss

1. Effects of Microcurie Doses of Iodine 131

Large numbers of people receive doses of iodine 131 at the microcurie level for medical diagnostic purposes. The general population in states not adjacent to the Nevada Test Site receive measurable doses at the picocurie level from radioactive fallout and nuclear technology. This study is directed at revealing the effects of microcurie doses of iodine 131 in children less than 16 years old. During the past year Research Branch developed rosters from cases at medical centers in the U. S. which describe populations that have had diagnostic iodine-131 exposure. Index cases were found and located in 16 hospitals in various parts of the country that also had AEC licenses to administer isotopes. The following figures were derived from the 2,028 cases identified and located for this pilot study:

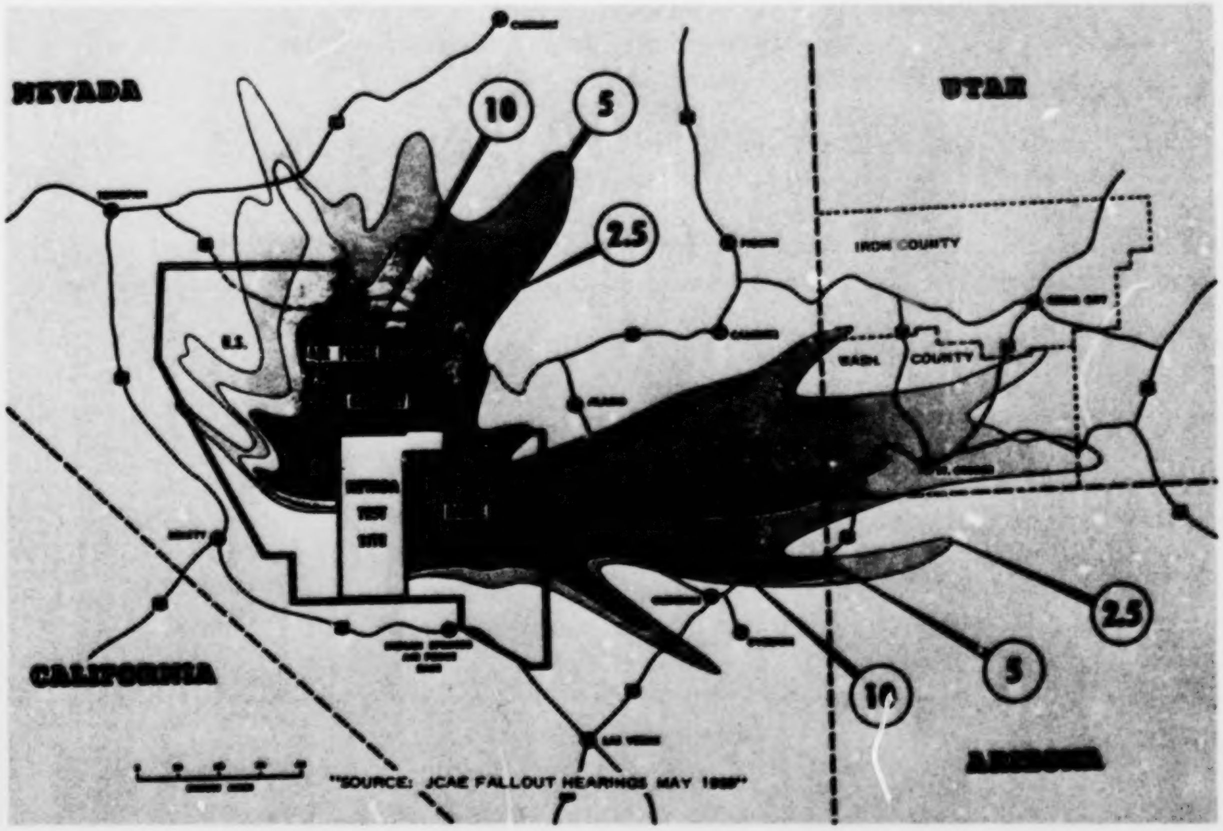
11% of the population were euthyroid at the time they were given the isotope,
30% of this same group were diagnosed as having thyroid disease,
59% had a variety of chronic diseases (constitutional).

2. Thyroid Anomalies in Utah and Nevada Children

There is evidence that residents of certain parts of Utah and Nevada may have been exposed to relatively greater amounts of fresh fission products from nuclear detonations at the Nevada Test Site since 1951 than population groups in other parts of the country (Figure 27). In May 1953, Washington County, Utah, is reported to have received an unusually high amount of radioactive fallout from a nuclear test at the Nevada Test Site.

The Joint Committee on Atomic Energy Hearings of 1963 directed specific attention to the hazards of iodine 131. During the past year Research Branch conducted field studies in Utah to ascertain whether or not any deleterious effects can be observed on the thyroid glands of children who were infants or in utero at the presumed time of high exposure. The exact dosage of iodine 131 from fallout is not known but estimates allow for iodine-131 doses to the thyroid gland to range from 10 rad to more than 400 rad.

Examination of about 2,000 children at three different locations in Washington County, Utah, revealed several thyroid abnormalities but none that can be specifically ascribed to radiation as an etiological agent. Because Washington County residents seem, historically, to have had a relatively high normal prevalence of thyroid disease, and because the more severe abnormalities were found both in children who were nonresident in Washington County in May 1953 as well as in children who were residents, it is not possible, from this particular study, to ascribe any degree of significance to radiation exposure. The question of residence in Washington County, Utah, in May 1953 may be of little or no importance in the present study if, indeed, the exposures to iodine 131 from fallout through the past several years were of significance throughout the state of Utah rather than confined to Washington County, because most of the children examined were lifetime residents of Utah.



"SOURCE: JCAE FALLOUT HEARINGS MAY 1959"

Figure 27. Estimated Radiation Dose in Roentgens from Nuclear Tests through 1958.

From a statewide collection of thyroid surgery records for Utah residents under 30 years of age during the 15-year period 1948-1962, the following observations were made:

1) The annual rate of thyroid surgery has been constant at 25 per 100,000 females under age 30, and 4 to 5 for males.
2) Surgery for toxic goiter has decreased approximately 50% during the study period.
3) Thyroiditis increased twofold and thyroid cancer increased almost fourfold.
4) The cancer increase was observed for both sexes primarily in the 20- to 29-year age group.
5) Observed frequencies of thyroid cancer were compared with expected numbers derived from other incidence studies. These numbers suggest an excess in Utah most marked in the most recent five-year period.
6) Continued study is needed to determine whether this excess of thyroid cancer is truly occurring in Utah and, if so, what genetic or environmental factors may be associated with it.

3. Tumors Following X-Ray Therapy for Benign Conditions in Man

This follow-up study will elucidate the effects of X-ray therapy on children who were irradiated for enlarged thymus and other nonmalignant head and neck syndromes occurring frequently in children.

A contract was negotiated in 1965 with the Massachusetts General Hospital, Boston, to reexamine a roster of children that had previously been studied for tumor frequency following therapeutic irradiation. The results of that study were so different from other studies that it was deemed advisable to reanalyze the data. An attempt to locate the persons and determine their present medical status is to be undertaken as well. Studies are being carried out in Cincinnati and in Rochester with similar groups of children.

F. COOPERATIVE STUDIES OF LATE RADIATION EFFECTS IN MAN

A. W. Hilberg, G. B. Darling

The surviving populations of Hiroshima and Nagasaki, Japan, represent the largest number of humans directly exposed to radiation from atomic bombs. The U. S. Government in cooperation with the Japanese Government, maintains and operates the Atomic Bomb Casualty Commission (ABCC) to study long-term pathologic effects in this population.

The Public Health Service participates in the ABCC program to study the long-range effects of atomic radiation on the survivors in Hiroshima and Nagasaki. The seven PHS officers of Research Branch assigned to the ABCC conduct collaborative and independent research studies in the fields of morphologic effects of radiation and the epidemiology of radiation effects.

Of particular significance in the research studies of the ABCC has been the emergence of cytogenetics. In 1965 the Research Branch assigned a cytogeneticist to the ABCC in order to develop more fully the cytogenetic program concerned with the survivors in both Hiroshima and Nagasaki. During this past year the program in cytogenetics has produced several publications and is beginning to develop some specific results pertinent to the exposed survivors in both cities.

G. EPIDEMIOLOGY OF RADIUM DIAL PAINTERS

S. C. Ingraham

Several hundred employees of the dial painting industry that flourished just before and after World War I were exposed by ingestion and by inhalation to radium 226 and radium 228 (mesothorium) in the form of radioluminous dial paint. Approximately 200 of these individuals today have measurable body burdens of these radioactive substances and are being studied by medical, dental, X-ray, and laboratory examinations, whole body counting, and histopathology and radiochemistry studies of surgical and postmortem specimens.

The project, funded by the Atomic Energy Commission, began in 1958 and is now in the final phase of epidemiological data collection with statistical evaluation of the data underway. To date, of 362 radium cases contacted, 150 have completed the basic medical and radiation evaluation; an additional 51 have undergone at least one study. The remaining 161 known living cases have either refused to cooperate or are living out of the area.

H. THOROTRAST FOLLOW-UP STUDY

N. C. Telles

Thorotrast, colloidal thorium dioxide, was commonly used from 1930 to 1950 as a contrast medium for X-ray studies. This material was injected intravascularly and has been strongly implicated as the cause of liver tumors appearing in patients who received it. Because of its extremely long half-life, the high degree of retention in the body, the large number of radioactive daughter products, as well as considerable translocation of these daughter products, many experts think that, from a purely dosimetric viewpoint, Thorotrast might also increase the incidence of leukemia, bone sarcoma, and lung tumors in these same groups of patients. This study focuses its attention primarily on the morbidity-mortality aspects of those who received Thorotrast, and secondarily on the clinical changes following the use of Thorotrast.

In 1963 a pilot study of 437 Thorotrast recipients was begun at the University of Michigan. This study, completed in early 1965, developed certain materials and methods useful in tracing, recalling, and examining Thorotrast recipients. Ten subjects were studied in detail.

In June 1964, a contract was signed with the Massachusetts General Hospital to study approximately 150 Thorotrast recipients available there. Sixty-one of these are still living and are currently being recalled for a complete physical examination, clinical laboratory evaluation, X-ray examination, cytogenetic studies, and whole-body counting. To date, 22 of these Thorotrast subjects have been referred to the Northeastern Radiological Health Laboratory by the hospital for whole-body counting. The patients recline on a cot that was constructed specifically to position their bodies in a meter arc, and are counted using an 11- by 4-inch detector (Figure 28). Although the data from these subjects are still being analyzed, a number of points can be made initially:

1) It appears from the preliminary data that the dose injected many years ago can be correlated with the body burdens just obtained using the NERHL system.
2) It appears that the values are in the same range as reported by other workers.
3) There is a possibility that the majority of the injected Thorotrast can be accounted for using whole-body counting techniques.

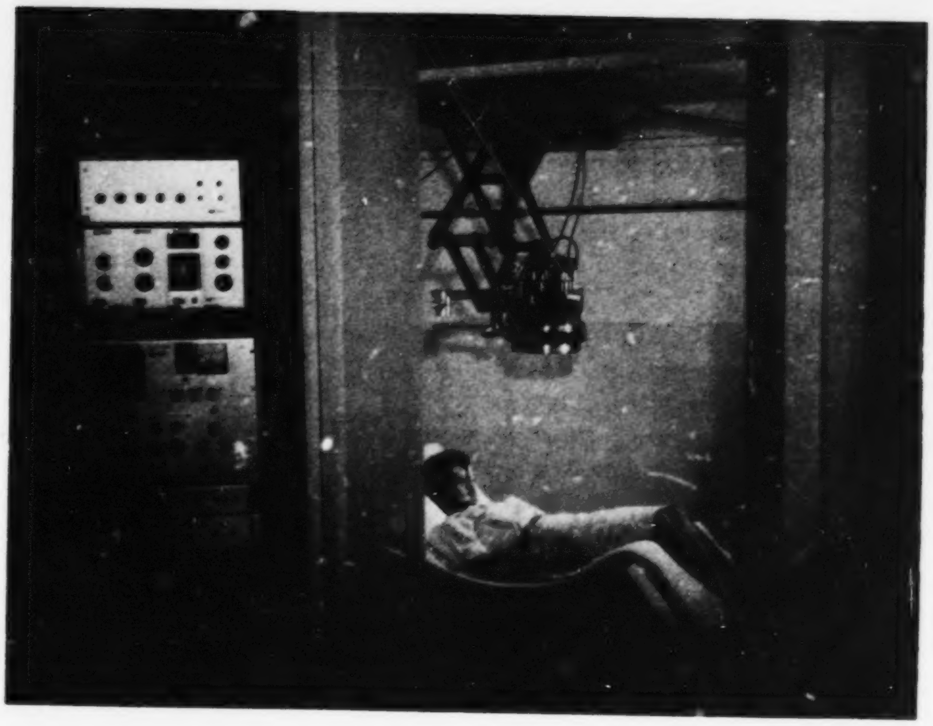


Figure 28. Low-Level Shielded Counting Facility at NERHL.

The retention of ^{232}Th in the liver and spleen is well established, but the levels of its daughter products throughout the body are not clear. In addition to determining body burdens, distribution of activity within the body is being studied; i.e., deposits at injection sites, and wash-out products in fecal and blood samples.

As a concurrent investigation into the overall study of the effects of Thorotrast in man, a cytogenetic laboratory was established at the Northeastern Radiological Health Laboratory to examine peripheral blood. After analyzing many cases, some correlation may be made between body burden and observed radiation-induced chromosome aberrations in human cells.

Other medical facilities in the United States may be able to furnish further patient material to NERHL from their rosters, enabling the laboratory to study a greater number of cases. This would allow a better evaluation of the amount of thorium retained in the body, its distribution, and its relation to clinical effects, including chromosome aberrations.

In February 1965, a contract was signed with the University of Cincinnati School of Medicine to study the relationship between Thorotrast scarring and tumor incidence, as well as the microdistribution of Thorotrast in organs, especially the bone marrow. This will provide a better basis for determining bone and bone marrow doses from Thorotrast and its daughter products. The University will avail itself of old and new material provided by the Massachusetts General Hospital and other institutions throughout the country where Thorotrast was used.

I. REGISTRY OF RADIATION PATHOLOGY

A. W. Hilberg

The Registry of Radiation Pathology collects relevant pathologic materials from all over the world to serve as a medium for study, stimulus for research, and as a reference for comparison. The work includes collecting, classifying, collating, and analyzing material related to low-level long-term radiation effects and isotope exposure. The unit also screens and organizes material into study and teaching files, participates in radiology and relevant radiation pathology lectures and graduate courses, and conducts weekly seminars in radiation pathology.

The Registry of Radiation Pathology was established in 1962 at the Armed Forces Institute of Pathology, Walter Reed Army Hospital, through the sponsorship of the Division of Radiological Health of the U. S. Public Health Service. It operates under these auspices and is staffed by both the Army and PHS.

Two study sets have been completed during the past year: "Comparative Study of Four Fatal Cases of Total-Body Radiation," and "Plutonium Inhalation in the Dog." Two other study sets are in preparation: "Hiroshima and Nagasaki in Retrospect - An Evaluation of Physical and Biological Effects," and "Radiation Injury - A Comprehensive Study of the More Important Lesions."

During the year, 358 new cases have been coded and entered in the registry. Of those, 95 were considered appropriate as teaching cases with extra slides prepared and detailed clinical summaries made. This brings the total cases in the registry to 1424, 869 human cases and 555 veterinary cases. Of the total cases 139 have been coded as having had isotope therapy or contact. A recent change in accessioning procedures has provided the registry with many additional current cases that might not have otherwise been reviewed by the staff.

Specific research problems investigated by the registry staff have been based upon primary mechanisms of radiation injury and factors that tend to modify these responses. An intramural research project, "Serum Enzyme and Pathologic Changes After Whole-Body Irradiation and Effect of Partial Shielding Protective Agents," has recently been initiated.

Continued work upon the "Atlas of Radiation Pathology" centers primarily about effects relating to the skin and accessory structures, endocrine organs, respiratory system, digestive system, and central nervous system.

J. RADIATION REGISTRY OF PHYSICIANS

J. Westlake

The Radiation Registry collects resource data for studies designed to gain knowledge regarding the long-term effects of ionizing radiation in man. The data are provided through questionnaires completed by members of the American College of Radiology and members of the College of American Pathologists. The original group consisted of 4,743 radiologists and 3,123 pathologists who were members of their respective Colleges and residents of the United States as of December 1961. To date 90% of these radiologists and 77% of the pathologists have submitted completed questionnaires. As new members are admitted to the Colleges, their names are included in the Registry. Through December 1965, 1,012 radiologists and 1,600 pathologists, who were United States residents, were added. Of these members 63% of radiologists and 51% of pathologists have responded.

Detailed coding of each questionnaire generates at least 10 data cards. This phase of the procedure for the original group was nearly completed at the end of 1966. The data are to be transferred to magnetic tape, and specifications for tape edit are to be prepared and programmed. The corrected tape should be available for output of selected tabulations by May 1, 1967.

The statistical unit plans to code the questionnaires for members admitted after the original group. They will code and analyze the data obtained from those physicians who reside in foreign countries, and have started sorting death certificates received from the American Medical Association to obtain those for former members of the Registry. There are plans to obtain certificates for those deceased members whose records are not included in the AMA group.

V. ENVIRONMENTAL SCIENCES

A. REMOVAL OF RADIONUCLIDES FROM FRESH MILK

1. Fixed-Bed Commercial Plant

R. E. Bales, G. K. Murthy, J. E. Campbell

In the event of long-term radiological contamination of milk over a wide area, a practical system for removing radioactivity from large quantities of fluid milk would be an important means of salvaging fresh milk for the consumer market.

Studies conducted by Research Branch have culminated in the development, construction, and successful testing of a fixed-bed commercial-scale ion-exchange plant for removing both cationic and anionic radionuclides from fluid milk. A pilot-scale plant using the moving-bed ion-exchange principle has also been developed and constructed for this same purpose. These accomplishments are the result of a joint effort over the past several years by the U. S. Public Health Service and the U. S. Department of Agriculture.

In 1960, a pilot plant with a capacity of 100 gallons per hour was constructed to refine the previously developed laboratory ion-exchange process with a view to adapting it to commercial use. The pilot plant demonstrated that the fixed-bed, cation-exchange system would effectively reduce the radiostrontium in fluid whole milk to acceptable levels without impairing the cation composition, the flavor, or nutritional components of the treated milk. A commercial-scale plant, designed to remove strontium from milk at a rate of 12,500 pounds of milk per hour, was then constructed under contract with Producers Creamery Company, Springfield, Missouri. Since its completion in 1964, more than 1,200,000 pounds of fresh whole and skim milk have been processed for strontium removal, thus demonstrating the commercial feasibility of the process.

While the strontium-90 removal system was being evaluated in the pilot and commercial-scale plants, laboratory investigations continued for the development of methods to remove radioactive anions, principally iodine 131, from milk by ion-exchange (Figure 29).

At the time the full-scale tests on the strontium-90 removal plant were being completed, the laboratory investigations indicated that anion removal by ion-exchange also had potential full-scale application. Therefore, under sponsorship of the Public Health Service and the Department of Agriculture, a contract was let in 1965 with the same commercial milk processor to design and build an ion-exchange column to remove iodine 131 from milk and to incorporate it into the existing full-scale plant (Figure 30). The contract also included testing of the resulting plant to confirm the feasibility of the combined strontium-iodine removal process.

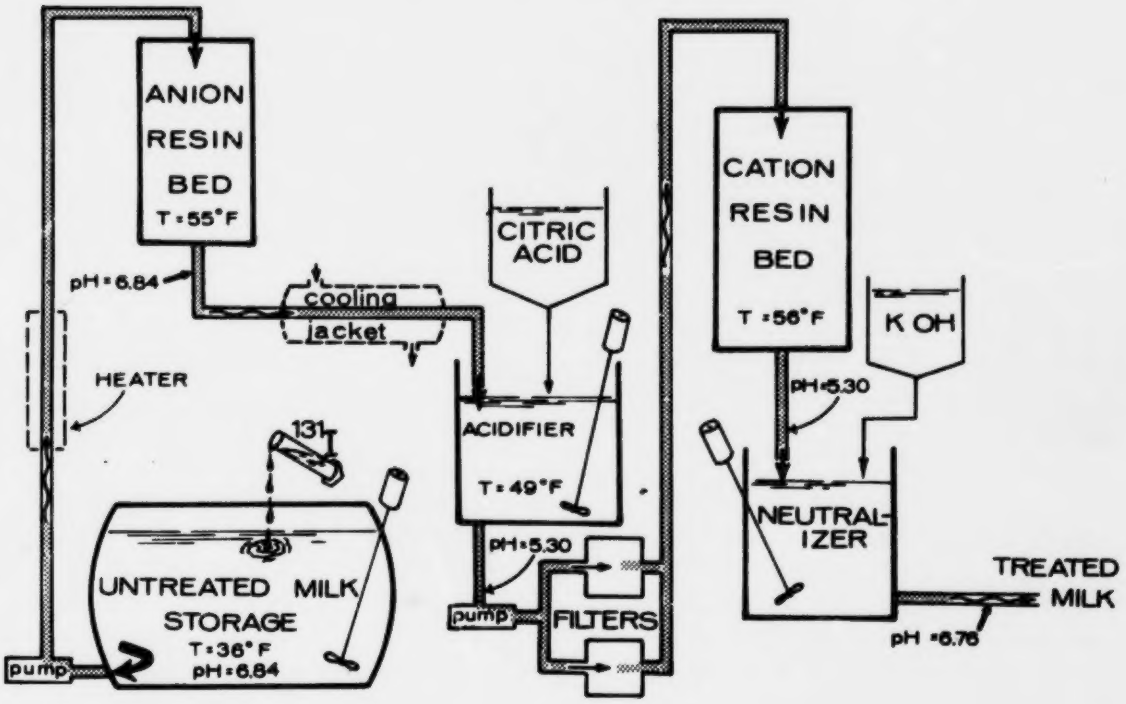

ANION RESIN BED
T=55°F
pH=6.84
cooling jacket
HEATER
131I
UNTREATED MILK STORAGE
T=36°F
pH=6.84
pump
CITRIC ACID
ACIDIFIER
T=49°F
pH=5.30
pump
FILTERS
CATION RESIN BED
T=56°F
pH=5.30
K OH
NEUTRALIZER
TREATED MILK
pH=6.76

Figure 29. Laboratory-Scale Fixed Bed Cation-Anion Exchange System.

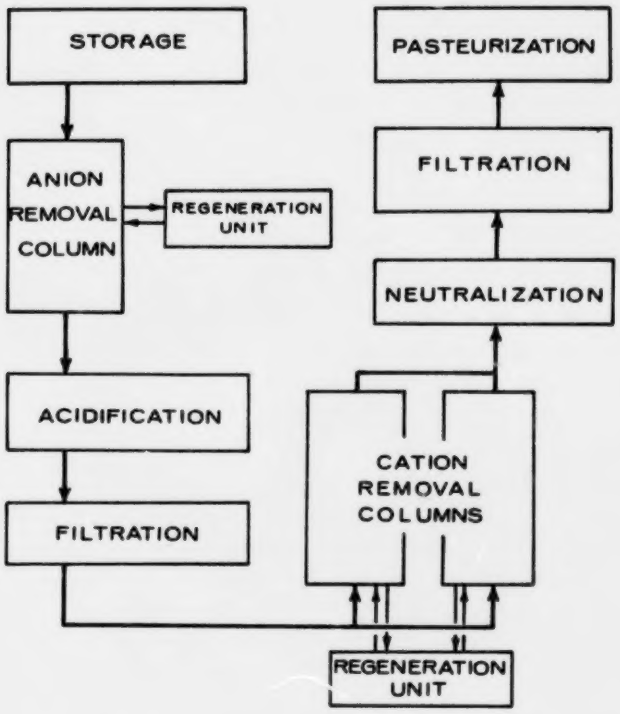

STORAGE
ANION REMOVAL COLUMN
REGENERATION UNIT
ACIDIFICATION
FILTRATION
CATION REMOVAL COLUMNS
REGENERATION UNIT
NEUTRALIZATION
FILTRATION
PASTEURIZATION

Figure 30. Scheme of Full-Scale System for Removing Radionuclides from Milk.

After extensive preliminary testing, three full-scale tests of the system were made in May and June 1966. About 100,000 pounds of fresh milk were processed in each test at approximately 20,000 lb/hr, nearly 50% more than the design flow rate of the cation system. The milk was labeled with 2,000 pCi/liter of iodine 131 and 3,000 pCi/liter of strontium 85, as environmental levels of both iodine 131 and strontium 90 in the raw milk were too low to determine the efficiency of radionuclide removal accurately.

The process removed more than 99% of the iodine 131 and 91% of the strontium 85. Chemical analyses indicated that the differences in chemical content between the raw and processed milk were not significant. No bacterial problems were encountered, and the milk composition analysis showed nothing unusual.

The full-scale plant has shown that iodine 131 and strontium 85 in large volumes of fresh fluid milk can be effectively reduced without seriously changing the organoleptic, chemical, or microbial quality of the milk, and without significant operational problems. Feeding studies are now underway to assess the nutritional quality of the milk product from the combined process. It appears that removal of cations (strontium) adds about 2.2 cents per quart to the cost of milk, and removal of radioiodine simultaneously would increase the cost by about 1.6 cents per quart, for a total increase of about 16% to the consumer.

2. Moving-Bed System
R. E. Bales, J. P. Walker

Extensive laboratory studies have indicated that the Higgins continuous ion-exchange contactor may also be useful in removing radionuclides from milk. In this process an ion-exchange resin bed continuously moves counter-current to the flow of milk through a closed (folded loop) system as part of it is regenerated in another section of the system (Figure 31).

In 1964, the Public Health Service and the Department of Agriculture jointly sponsored construction of a moving bed ion-exchange milk treatment plant, based on the Higgins patent. The plant has a capacity of 7,000 pounds of milk per 8 hours and consists of two continuous ion-exchange contactors, one to remove radioactive cations and one to remove radioactive anions. The resins are the same type used in the full-scale fixed-bed plant. The plant is self-contained (except for power supply) and can be installed in a standard 40- by 8-foot truck trailer to make it readily transportable (Figure 32).

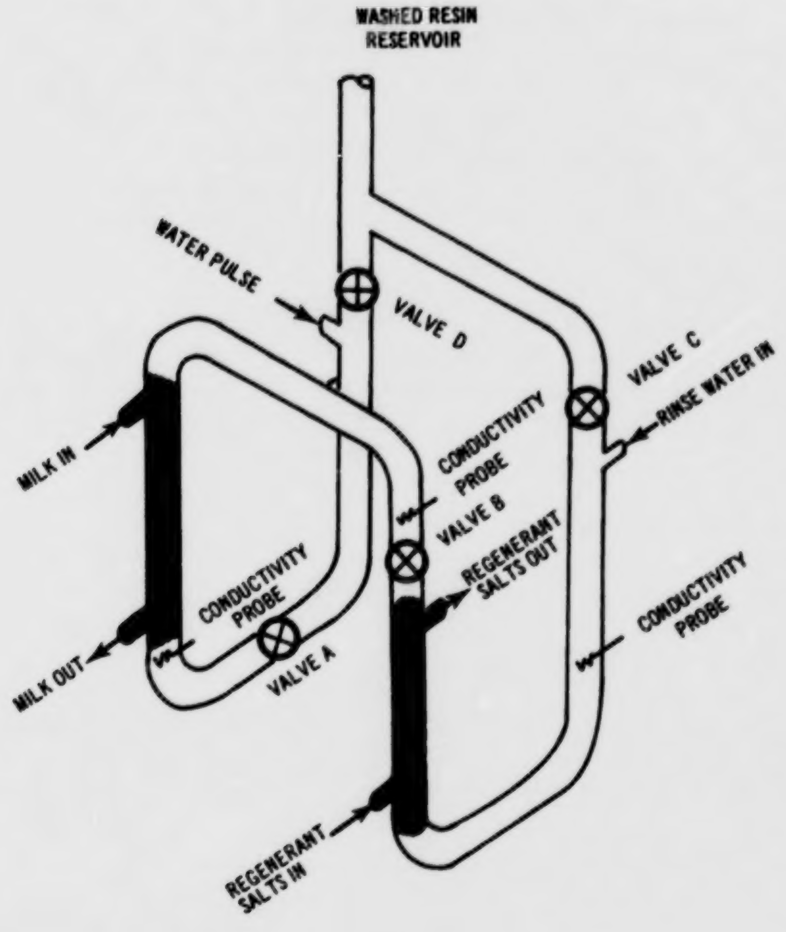

WASHED RESIN RESERVOIR
WATER PULSE
VALVE D
VALVE C
RINSE WATER IN
MILK IN
CONDUCTIVITY PROBE
VALVE B
REGENERANT SALTS OUT
CONDUCTIVITY PROBE
VALVE A
MILK OUT
CONDUCTIVITY PROBE
REGENERANT SALTS IN

Figure 31. Moving Bed Ion-Exchange Folded-Loop Arrangement for Milk Decontamination Pilot Plant.

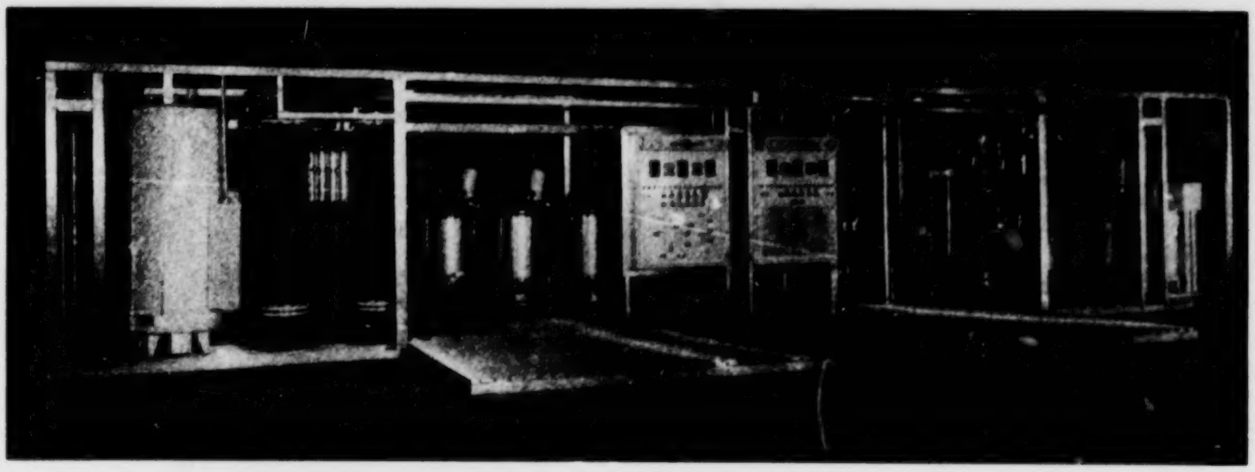


Figure 32. This Pilot-Scale Moving-Bed System Can Be Installed in a Standard 40- by 8-foot Truck Trailer.

The pilot plant is scheduled to be operated at the Southeastern Radiological Health Laboratory in Montgomery, Alabama. The plant testing program will include evaluation for efficiency of radionuclide removal, product acceptability (in terms of taste, odor, and appearance), product alteration, and sanitary quality. As the operation becomes refined, nutritional testing and chemical analyses of the treated milk are planned, using methods similar to those used in evaluating the product from the full-scale fixed-bed plant.

The two existing plants may be used in the near future in the development and refinement of lower-cost treatment techniques or treatment of milk massively contaminated. It is emphasized, however, that the objective in developing these processing plants is to provide the capability to treat contaminated fresh whole milk for immediate human consumption. To this end, formal approval by the U. S. Food and Drug Administration has been requested so the full-scale fixed-bed unit could be used for this purpose on an emergency basis. Extensive testing has been undertaken to insure the wholesomeness of the product. Similar approval will be sought for the moving-bed process at the appropriate stage in its development.

B. ENVIRONMENTAL RADIATION EXPOSURE STUDIES

1. Background Gamma Survey of Communities in the United States
R. K. Stoms, S. G. Levin

Measurements of background radiation using portable gamma scintillation counters (PGSC) and the Shonka tissue equivalent chamber--considered to be the most accurate instrument available for directly measuring dose to tissue--have been made in 53 cities in Colorado, Michigan, and Minnesota.

Six different PGSC instruments were used and each was referred to one used simultaneoulsy with the Shonka chamber; the Shonka chamber was calibrated in microrads per hour using radium. After all calibrations were completed, each of the PGSC measurements from each of the towns was converted to microrads per hour. Then an average, a variance, and a frequency distribution were calculated for each town, and the towns ranked according to background levels. This information, transmitted to the University of Minnesota in July 1966, completed the Research Branch part of the Tri-State Congenital Malformation Study (see p. 62).

2. Identifying Community Water Supplies Containing Radium 226 and 228
J. L. S. Hickey, S. D. Campbell

An earlier Research Branch study (the Midwestern Environmental Health Study) attempted to demonstrate whether elevated bone sarcoma rates prevailed in persons who ingested more than 3 pCi of radium 226 per liter of drinking water. However, the populations involved in those studies were too small for the observed difference to be declared statistically significant. The present project was undertaken to find larger population groups who have ingested high levels of environmental radium 226 and radium 228 from water. Recent research indicates that ingestion of radium 228 may have as much or more effect on bone than ingestion of radium 226.

In this study, Research Branch selected municipal water supplies to be analyzed for radium 226 and radium 228 at the Radiological Laboratory in Farmington, New Mexico, under contract with the State of New Mexico. Water samples have been collected from the municipal supplies of 1,000 cities in 20 states in an attempt to locate supplies having concentrations of 10 picocuries or more per liter. Where high levels of radium 226 and 228 are observed, additional samples will be collected to confirm the analysis.

The principal end product of this project will be a list of population groups who consume water containing various levels of radium 226 and radium 228. The study will also identify communities with virtually no naturally occurring radium in their water supplies. Persons from the latter communities could be selected to serve as controls in other radiological studies.

3. Bionomical Investigations

A. R. Garrett, S. L. Cummings

Of direct concern to the Environmental Sciences Section is the mechanism of radioisotope uptake and binding in plants. Investigations in this field will yield information regarding (i) the intricate relationships between multifactored soil systems and plant uptake mechanisms for radionuclides, (ii) specific correlations between radionuclide levels in biological media and substrate systems, and (iii) development of criteria for predicting the extent of radionuclide contamination in food chains from single events, and for evaluating the various effective measures that reduce the contamination of man's food chain.

Soils and minerals from different areas of the United States are being studied to determine the effect of their mineralogical content on the absorption and release of biologically important radionuclides. Some plants, consumed either directly or indirectly by man, may selectively absorb minerals or radionuclides present in the soil. To study this phenomenon in the food chain, several soils and commercial minerals from different parts of the United States have been analyzed for their mineralogical content. To date, seven commercial minerals and twenty-four soils have been analyzed for vermiculite, extractable cesium 137, and nonexchangeable cesium 137. Attempts have been made to relate the percentages of cesium to the percent of vermiculite using concentrations of carrier-free cesium of approximately 0.2 μCi per 100 milligrams of sample. A complete mineralogical analysis of the more abundant minerals has been completed on three commercial minerals and three soils. The analysis quantitates amorphous material, chlorite, kaolinite, mica, montmorillonite, quartz, vermiculite, and K-feldspar.

4. Radioiodine Field Investigations

D. S. Barth

The Radioiodine Field Investigations Project conducted jointly with AEC attempts to quantitate the extent of radioiodine exposure to humans. Before this project began, abundant evidence suggested that radioiodine resulting from nuclear explosions or reactor operations may approach the Radiation Protection Guide (RPG) levels before either external radiation or other specific radionuclides.

Adequate quantitation requires accurate assessment of atmospheric concentrations including chemical form and particle characteristics;

atmospheric transport mechanisms; ground deposition characteristics; mechanisms of food chain uptake, including concentrations in milk resulting from dairy cow uptake; and the resultant dose in humans from inhalation and other routes of entry. These data provide an accurate foundation on which to base the Radiation Protection Guides.

Some unusual research facilities are used to collect data for this project. Among these are a dairy farm; a beef herd and experimental farm; a mobile radioassay unit, with a wide-beta system and a gamma spectrometer with an opposed 4- by 9-inch crystal detector; and mobile micrometeorological monitoring units (Figures 33 and 34). With these facilities controlled ingestion and inhalation studies can be conducted with a dairy herd at a fixed location; similar studies can also be carried out at remote locations where sources of radionuclides are generated, with meterological data accumulation and counting capabilities available at that site.

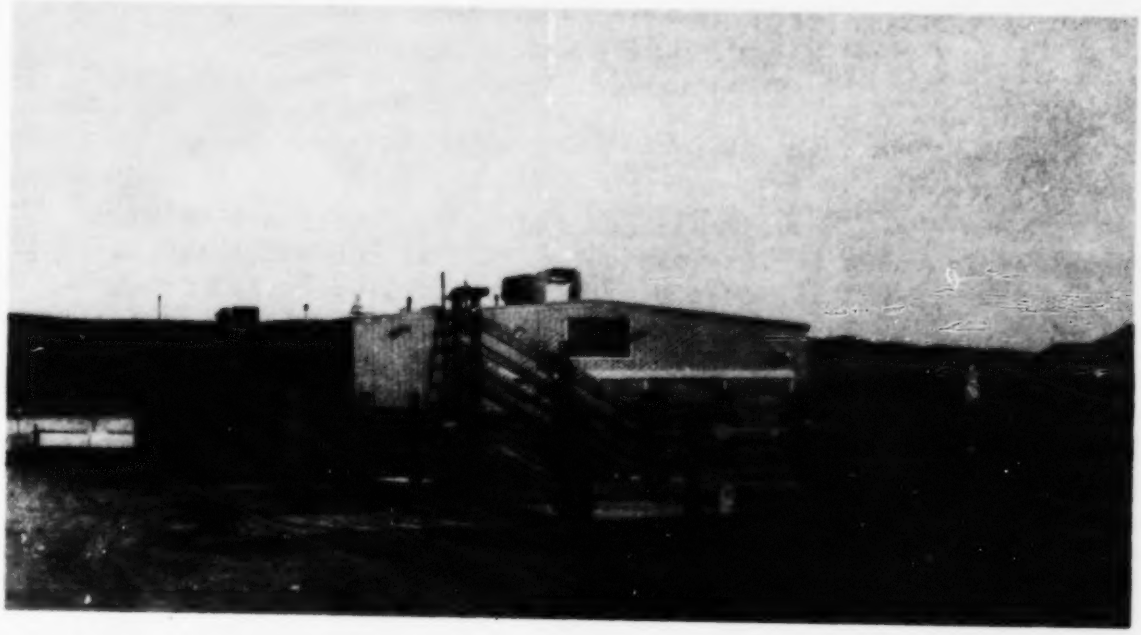


Figure 33. USPHS Farm Laboratory Located in Area 15, Nevada Test Site.

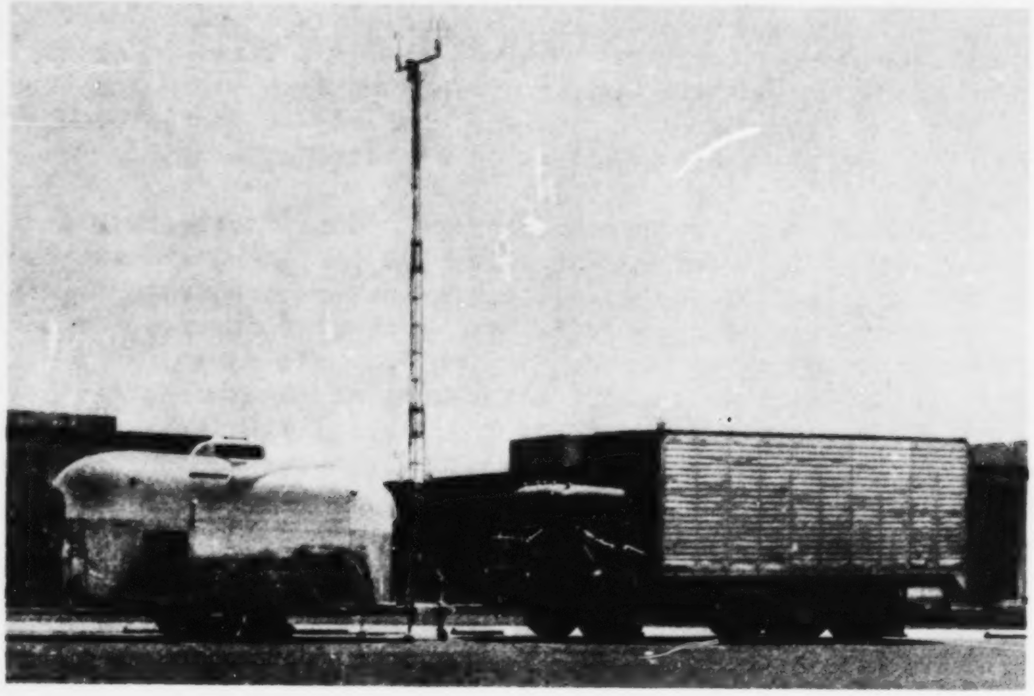


Figure 34. Micrometeorological Monitoring Trailer and Radioassay Truck.

Field studies have been conducted in conjunction with USAEC testing of underground nuclear explosives and of nuclear reactors at the Nevada Test Site. In addition, three controlled experiments have been completed using the dairy herd. One study investigated the metabolism of a mixture of iodine 131 and iodine 126, and two others involved controlled release of an iodine-131 tagged dry aerosol over the experimental farm with subsequent inhalation and ingestion studies on the dairy herd. These studies elucidated the variance of iodine concentration in milk from cows ingesting iodine after deposition on various types of forage or inhaling the iodine.

The studies, in general, have been multipurposed and have resulted in improved methods of air, soil, and forage sampling. Other factors examined in each study were effects of micrometeorological variables, particle-size effects, radionuclide deposition on soil and various forages, and effects of irrigation. Finally, the studies have yielded information on the kinetics of radionuclide uptake and secretion in milk through various routes of entry in the dairy cow.

5. Biological availability of Aged Mixed Fission Products and Neutron Activation Products

D. S. Barth

Since atmospheric testing has ceased, fresh fission products are less prevalent in the general environment, but the store of aged fission products and certain neutron activation products will remain for some time. Also, because tests for peaceful application of atomic energy involve more fusion than fission reactions, the amount of activation products in the biosphere may increase. The biological availability of these kinds of radionuclides must be explored to determine what hazard exists and to provide data for an accurate assessment of man's total environmental radiation. This investigation makes use of a unique facility, an experimental farm located near the Sedan crater, where fission and activation products produced by a nuclear detonation are available for uptake in crops. Preliminary work has included mapping and soil sampling of the farm. Physical, chemical, and radiological descriptions of the soil samples are in progress. Some of the soil samples are being used for leaching and plant uptake studies. The milk from dairy cows consuming forage grown on the farm is also being analyzed for aged fission and activation products, as is the forage.

6. Radionuclides in Domestic Animals and Wildlings

D. S. Barth, R. E. Engel

The goals of this project are (i) to determine the concentrations of mixed fission products in domestic animals, edible wildlife ruminants, game fowl, and aquatic species in the Nevada Test Site (NTS) environs, (ii) to maintain veterinary public relations for the AEC, and (iii) to investigate alleged damage to domestic animals as a result of AEC activities. The goals are met by routine and special sacrifices of the NTS beef herd, wildlife ruminants (mule deer in particular), fowl, and fish. Biological samples for gamma spectroscopy, radiochemical analysis, and histopathology are frequently taken in cooperation with personnel from the University of Nevada.

The routine sacrifices provide nine different tissue samples which are analyzed for calcium, potassium, and nine of the most important radionuclides. The nine tissues plus an additional nine are also examined for microscopic changes consistent with radiation damage. Additional studies are in progress to determine grazing habits and plant preference of beef cattle on desert ranges during each season of the year.

The data collected are arranged to show seasonal levels of radionuclides in the tissues and organs of various ruminants and the variation among species and areas. This information is being used as background data in connection with various inquiries from ranchers, wildlife management people, and animal welfare agencies.

To date, fission product levels have remained at or near background levels in all tissues and organs examined except for radioiodine in the thyroid. No effects attributable to radiation have been detected by gross or microscopic examination of tissues from beef cattle or wildlife ruminants.

C. DOSIMETRIC STUDIES OF NATURALLY OCCURRING RADIONUCLIDES

1. Radiometrics

a. Facilities

B. Branson, W. J. Averett

The Radiometrics Group serves the Radiological Health Research Activities at the Robert A. Taft Sanitary Engineering Center with a centralized counting facility, maintains all counting equipment, and develops systems with improved sensitivity. Persons in the group also provide assistance and training to other DRH and Government agencies having similar requirements.

The radiometrics group maintains a low-level shielded facility (Figures 35 and 36) and low-background beta counters, large gamma detectors, and low-energy gamma detectors. An absolute air filtering system holds the low-level counting rooms under positive pressure, thus reducing and stabilizing radon-thoron background contributions to the counters.

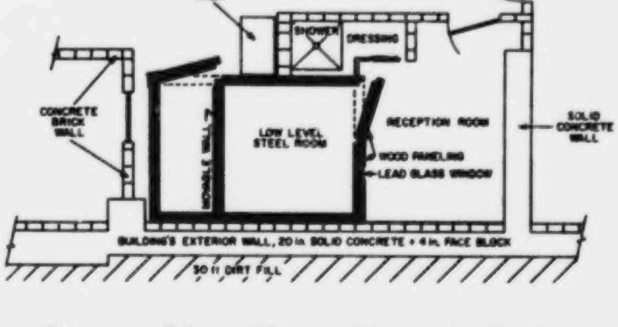

STAIRS UP
INSTRUMENTATION AREA
SHOWER
DRESSING
CONCRETE BRICK WALL
LOW LEVEL STEEL ROOM
MOVABLE WALL
RECEPTION ROOM
SOLID CONCRETE WALL
WOOD PANELING
LEAD GLASS WINDOW
BUILDING'S EXTERIOR WALL, 20 in. SOLID CONCRETE + 4 in. FACE BLOCK
30 ft DIRT FILL

Figure 35. Floor Plan of Typical Low-Level Shielded Facility.

Figure 36. Low-Level Shielded Counting Room at RHRA.

A new three-detector gamma system is being evaluated. The largest detector is a NaI(Tl) annulus crystal (10 inches in diameter and 12 inches long, with a 4 3/4-inch inside diameter); two 4- by 4-inch NaI(Tl) crystals face each other inside the annulus. This system is connected through a high resolution coincidence-anticoincidence gating system to a multichannel analyzer. These three detectors may be coupled into many gating combinations for decay scheme studies, absolute standardizations, and separation of complex mixtures. One of the simplest arrangements is with the two 4-inch crystals summing and the annulus in anticoincidence. The result is an efficiency approximately twice that of a single 4-inch detector with the background noise reduced by a factor of three.

b. Whole-Body Counter Calibration for Measuring Potassium in Man

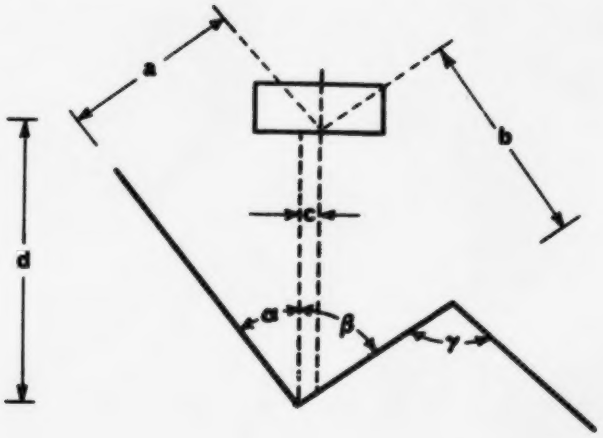
H. E. Kolde, R. J. Velten, L. E. Elfers, W. M. Cox

A human phantom consisting of fifteen 10-pound sugar bags was designed for calibrating ten radionuclides generally distributed in man. Adequacy of its design was based on comparisons of in vivo and in vitro potassium-40 calibration values and spectral shapes. In 90 whole-body scans of radiation workers from a local establishment, 15 were found to contain radioisotopes other than cesium 137 and potassium 40. One individual revealed burdens of cobalt 60, zinc 65, zirconium 95 - niobium 95, and tantalum 182. The computer program for the matrix method of unscrambling gamma spectra with the residual analysis feature was modified for solving complicated human spectra. A rapid screening procedure was developed to identify individuals accidentally exposed to radioactivity.

c. Intercalibration of Three Whole-Body Counters for Potassium in Man

G. J. Karches, H. E. Kolde, H. N. Wellman

Whole-body counters at the Radiological Health Research Activities, Cincinnati General Hospital, and Wright-Patterson Air Force Base were intercalibrated for measuring potassium in man. The design of the three counters is similar--large steel rooms, single 8- by 4-inch NaI(Tl) detectors, and tilting chair geometry (Figure 37). Approximately 2.5 μCi of ^{42}KCl were administered intravenously to 10 normal adult male volunteers ranging in weight from 60 to 129 kg. Attention was given to the techniques for determining the activity of the injected potassium 42 and measuring injection and excreta losses. The effects of gamma-emitting impurities, especially arsenic 76, were also determined



Geometry	Cincinnati General Hospital	Sanitary Engineering Center	Wright-Patterson Air Force Base
a, cm	51.0	47.0	46.0
b, cm	43.5	45.0	46.0
c, cm	0	-1.0	0
d, cm	59.5	57.0	65.0
α	50°	45°	45°
β	41°	42°	45°
γ	97°	97°	90°

Figure 37. Subject-Detector Geometry at Three Different Facilities in the Cincinnati Area.

Analysis of variance of all potassium data indicated that one facility averaged 4% higher than the other two at the 95% confidence level. The internal precision within each laboratory was 6% at the 95% confidence level. Phantoms simulating various body builds showed good agreement with the in vivo data for lean to average weight persons, but was poor for the overweight individual. Weight appeared to be as reliable as any other body-build expression.

d. A Sensitive Technique for Measuring Thyroidal Uptake of Low Doses of Iodine 131

H. N. Wellman, T. B. Yeager, G. J. Karches

A sensitive technique for measuring much lower doses of iodine 131 than usual for clinical thyroid function tests has been developed. This procedure can also be used to measure low levels of iodine 131 accidentally incorporated into the human body. The detection system consists of two 3- by 1 1/2-inch sodium iodide (Tl) crystals coupled to 3-inch photomultiplier tubes, and is suspended from an apparatus that allows the crystals to be aligned in various reproducible positions (Figure 38). The crystals are usually placed with their flat surfaces in contact with the neck and at right angles to each other.

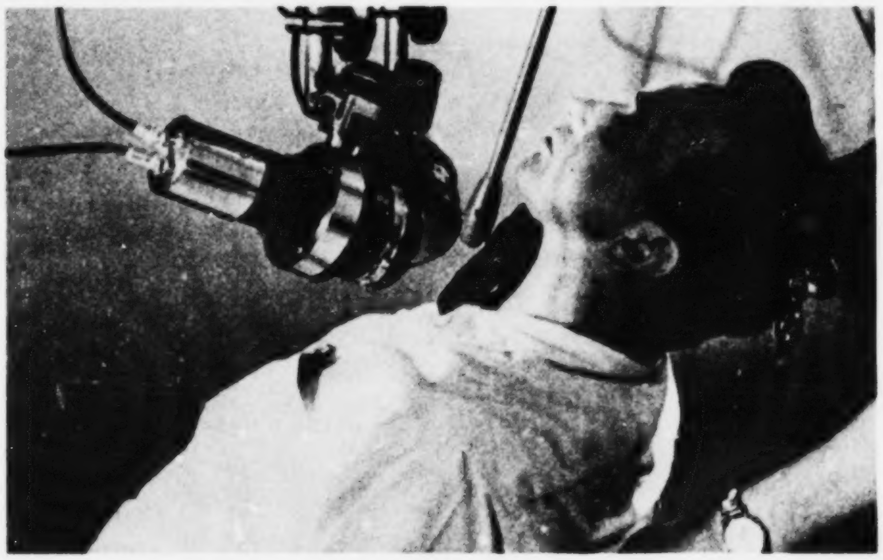


Figure 38. Subject Being Positioned at the Low-Level Shielded Facility for Thyroid Measurement by Two 3- by 1 1/2-inch NaI(Tl) Crystals.

Because of the proximity of the crystals to the thyroid gland, minor differences in the depth of the thyroid significantly affect the counting rate. These differences are corrected by correlating the ratio of photopeak to Compton continuum obtained in the patient with similar ratios obtained from a neck phantom having five inserts to simulate different depths. The standard is placed in the phantom to approximate a 20-gram thyroid having two lobes. In a steel shield, the lower detectable limit at the 95% confidence level is 50 pCi per gland for a 5-minute count. If the system is used outside the shield, the lower limit of detectability is increased by a factor of three.

Emphasis has been placed on correlating the results of this procedure to the usual standard clinical technique developed at the Oak Ridge Institute of Nuclear Studies. Evidence indicates that this method is more accurate in determining iodine uptake than the routine clinical procedure. Additionally, a very high Compton to photopeak ratio alerts one to substernal extensions of the thyroid. The method can be applied to children as well as adults.

2. Improvements in Gamma Spectral Analysis
S. Gold, J. Hardin, T. B. Yeager

For the past 5 years, gamma spectral analysis has provided continuous concentration values for particulates in ground-level air at Cincinnati. A similar technique has been used to analyze air filters collected from sampling stations throughout the United States. In an effort to improve the sensitivity of the technique, matrix analysis, the Radiological Health Research Activities procedure for analyzing gamma spectral analysis, was compared with a least squares technique to determine relative accuracy and sensitivity. No differences were observed under the conditions of this test.

A coincidence-anticoincidence counting system has been incorporated which will increase the sensitivity and extend the capability of gamma spectral analyses as applied to a variety of studies in progress in nuclear engineering and medicine, and radiobiology.

3. Beta Spectroscopy
V. Sodd, S. Jacobs, T. B. Yeager

RHRA scientists employ a high resolution beta spectrometer that uses a 110 mm^2 lithium-drifted semiconductor detector capable of absorbing beta particles with maximum energies up to 2.2 Mev. The resolution of this spectrometer for the 625 kev conversion electron of barium 137 is 4.0% at room temperature and 1.5% at -78° C. A coincidence system using an internal proportional counter gating device reduces the spectrometer background between 0 and 2.2 Mev to 0.45 cpm.

A least squares computer analysis program has been written for the simultaneous determination of complex beta spectra. This program is successful for samples containing two radionuclides.

4. Analysis of Human Bones for Strontium and Radium 226
A. Martin, E. Pinkston

About 80 human skeletons have been obtained from Marquette Medical School in Wisconsin from which selected specimens are to be assayed for distribution of stable strontium, strontium 90, and radium 226. The concentration of strontium 90 in three skeletons analyzed thus far was too low to measure presumably because the subjects, whose ages at death ranged from 64 to 75 years, lived only the last decade of their lives in the presence of fallout and because their bone mineral turn-over rates were low in old age. Cesium 137 was not measured because it is displaced by preservative solutions (see p. 56).

Analyses of skeletons believed to be high in strontium have been postponed so the entire collection could be surveyed for specimens having unusually high levels of stable strontium or radium 226. The results of the survey are not yet available for tabulation. A few skeletons high in strontium were discovered, but none seems to contain unusual amounts of radium 226.

5. Tritium Analysis

V. Sodd, B. Jacobs

Peaceful uses of atomic energy may localize large amounts of tritium (hydrogen 3) in the environment. Because of its low specific activity, tritium is difficult to detect and count accurately in environmental media. Therefore, samples containing tritium are often processed to concentrate the tritium prior to measurement.

Three 500-ml glass electrolysis cells used to enrich tritiated water have recently been calibrated for tritium analyses. For each cell, values for the volume reduction factor, activity increase factor, and tritium/hydrogen separation factor have been tabulated.

6. Heavy Elements

R. L. Blanchard, J. W. Kearney

Radon 222, a radioactive gas produced by the decay of radium 226, diffuses from the ground and is transported by atmospheric turbulence far from its origin through the troposphere and into the stratosphere. The radioactive decay of radon 222 and its short-lived descendants produces measurable quantities of lead 210 in the atmosphere. These lead atoms become attached to dust particles and eventually return to the earth's surface, primarily in rainfall.

Until recently lead 210 and polonium 210 were considered to be of lesser importance as components of our background radiation. According to recent reports, however, the internal dose delivered by polonium 210 to the general population may be a more significant component than previously estimated.

During investigations to determine the lead 210 content of human bone, a linear relationship between the concentration of lead 210 and strontium 90 was recognized. The linear correlation coefficient was determined to be 0.89. Such a strong correlation lends support to the hypothesis that lead 210 is an airborne contaminant and is related to fission product fallout through similar behavior of the two radionuclides in the atmosphere, and possibly relates to neutron activation from large-scale atmospheric weapons testing.

Assuming radioactive equilibrium between lead 210 and polonium 210 in bone, a relative biological effectiveness (RBE) of 10, and a uniform distribution of lead 210 and strontium 90 within the bone, the dose delivered by lead 210 and daughters to these bones is 3.4 times that delivered by strontium 90 and its daughter, yttrium 90.

Although a number of measurements and studies have reported the concentrations of lead 210 and polonium 210 in bone, relatively few measurements have been reported for human soft tissues. Consequently, measurements have been made of lead 210 and polonium 210 in kidney, liver, lung, pancreas, spleen, thyroid, and gonads from 20 individuals ranging in age from 6 to 78 years. Assuming uniform distribution of polonium 210 in the tissue and an RBE of 10, the dose rate in mrem/year is calculated to be numerically equivalent to the concentration of polonium 210 in the units of pCi/kg of tissue. Considering the possible genetic implications, the gonads possibly should be considered a critical organ for polonium 210.

High concentrations of lead 210 and polonium 210 observed in the Arctic Eskimo have been attributed to his food chain. These radionuclides are concentrated from air and rain by lichens. Caribou consume large quantities of lichens and constitute a substantial portion of the Eskimo's diet.

An analysis of various flora showed no significant difference among concentrations of polonium 210 and lead 210 found in lichens or mosses that grew in Alaska and those that grew in the central United States or in Denmark. Polonium 210 contributes nearly all (96%) of the alpha activity associated with these plants. The average polonium-210/lead-210 activity ratio was calculated to be 0.93 ± 0.05, very near radioactive equilibrium.

One sample of bluegrass from Ohio was included in this investigation for comparison. The polonium 210 and lead 210 found in the bluegrass was substantially less than that found in the moss and lichen samples. In addition, the ash content of lichens is considerably lower than that of grasses; consequently, animals may consume large quantities of lichens to obtain sufficient minerals. Animals grazing on lichens therefore appear to ingest considerably larger quantities of polonium 210 than those that graze on grasses more common to the northern temperate zone.

These investigations will continue during the next year to determine the concentration of lead 210 and polonium 210 in caribou meat, the intermediate link in the food chain of the Alaskan Eskimo.

D. ENVIRONMENTAL RADIOCHEMISTRY

1. An Integrated System for Sample Analyses and Data Handling

R. E. Bales

The demands of environmental studies require formidable numbers of samples to be accurately analyzed for alpha, beta, and gamma emissions. For these analyses, either a large number of analyzers is required, or a single system that will accept the required number of detectors and make use of common circuitry is needed.

Research Branch has contracted with Health Research, Inc., of Albany, N. Y., to develop and test a system capable of handling and presenting for interpretation a variety of complex data. The system accepts a number of detectors and uses common circuitry in its advanced design for radiological sample analyses and data handling. The system is designed for high speed and precision, and has the capability to handle concurrent radiometric data inputs from multiple sources including liquid scintillation counters, solid state detectors, alpha counting chambers, and crystal gamma spectrometers. It is compatible with the available telecommunications systems, automatic data processing machines, computers, and computer programs.

Practically all parts of the system have been completed except the portions of the random input signal handling relating to routing, and the portion of output format relating to digital-to-analog presentation. These portions, however, are complete in design and require only testing and approval.

The system is being tested for data entry, data production, transfer within the memory, and repeated exercising of the memory to assure that no structural change in the digital information occurs in the data handling transfer and other processing steps. The random input has been checked for ability to recognize an address position, to remove a word from the memory, and to augment this word and then return it to the memory in order that the mathematical process of spectrum assembly can properly be handled.

2. Effect of Binding Agents in Natural Feeds on the Radionuclide Uptake in Ruminants

R. E. Bales

About half of the human body burden of total radioactivity originates in milk and milk products, and another one-fourth from meat and animal products. Also, these substances constitute the main portion of a child's diet. Thus, there is special need to investigate ways of safeguarding the radioactive content of these substances in the food chain. One method is to determine how radionuclides that may contaminate animal feeds can pass through an animal's digestive tract without being absorbed. Preliminary evidence indicates that there may be substances in natural feeds that have an affinity for some radionuclides and that these substances may reduce the uptake of radionuclides by the animal body.

In contracted studies conducted at the University of Florida, six varieties of Bermuda grass hays were harvested at various maturities, and fed to two dozen wether lambs. Hays and feces were analyzed for dry matter, ash, strontium 90, cesium 137, and calcium and potassium to provide information on the percentage of dietary components excreted and ratios of feces to diet. Cesium to potassium ratios indicated that more of the cesium 137 is excreted by animals fed young Bermuda grass hay than by those fed mature hay. Analyses for strontium have not yet been completed.

Other feeding trials using six wether lambs fed diets of grass, legumes, or purified diets were aimed at gathering metabolism data on calcium 47 and strontium 85. Single oral doses of 40 microcuries of calcium 47, 100 microcuries of strontium 85, and 10 grams of chromic oxide were administered; blood, fecal, and urinary samples collected over 10-day periods were analyzed. The cumulative percent of strontium 85 excreted divided by the corresponding cumulative percentage of the chromic oxide, suggests a more rapid absorption and excretion of strontium 85 from Bermuda grass and purified diet than from alfalfa. Also, oral doses of strontium 85 were excreted faster in feces for Bermuda diet, and fecal activity decreased most rapidly for wethers fed the Bermuda grass. A greater total fecal recovery of strontium 85 was achieved when the alfalfa was fed.

3. Effects of Alginates on the Absorption of Radiostrontium

R. E. Bales

Because of the rapidly increasing use of nuclear materials for a variety of peaceful purposes with the concurrent increase in the production of radioactive wastes, steps are needed to prepare for accidental contamination of the environment and consequent exposure of people. Furthermore, the resumption of large-scale nuclear testing would increase the likeliness of radioactive contamination in the stratosphere.

The long-term hazards of fallout from nuclear explosions result from the uncontrolled dispersal of radioactive isotopes of the many elements produced by fission and fusion reactions. Radioactive products having short half-lives may decay before they cause extensive biological damage, but a few with long physical half-lives--notably strontium 90, cesium 137, and carbon 14--are of serious biological importance. Once deposited on vegetation, they may be ingested by man and by domestic animals that serve as a food source for man. Strontium 90 presents a special hazard because it is deposited in bone and is released from it extremely slowly. The effect of a chronic low-level dose of strontium 90 on human subjects, especially children, and the methods of preventing this damage, have received wide study. Such studies have necessitated a thorough understanding of the metabolism of strontium, most of which has been gained by analogy to the nutritionally essential element, calcium.

In 1964, researchers at McGill University in Montreal, Canada, reported that alginic acid derived from brown seaweeds selectively suppressed the absorption of radioactive strontium from ingested food material, thus permitting calcium to be available to the body. The Division of Radiological Health, through contracts administered by Research Branch, has subsequently supported this research.

Working with rats, McGill researchers have found alginic acid to be equally effective whether introduced into ligated intestinal segments, directly into the stomach by intubation, or mixed with food. With many preparations, strontium-90 absorption was reduced by as much as 87% while maintaining a positive calcium balance even on prolonged feeding. Administering sodium alginate as a jelly mixed with food overcame the problem of constipation, a significant finding with respect to the use of the compound in human subjects. Finally, a linear relationship was established between the dosage of the radioisotope and bone uptake in the presence of different levels of alginate, suggesting that the absorption of strontium is inhibited at the lower levels of intake of radioactive strontium.

Studies at RHRA using cats dosed with radiostrontium show alginate ingestion to increase the excretion rate of the endogenous radiostrontium (see page 55). Because alginates are a common ingredient in the human diet, studies of its effectiveness in reducing absorption or enhancing excretion of radiostrontium in man have also been developed at RHRA.

Mannuronic/guluronic acid ratios have been determined for algins prepared from a variety of marine algae from worldwide sources. The biological activity varies considerably between species. Calcium salts as well as degraded polysaccharides are being investigated for relative effectiveness. The calcium alginate has a mode of action similar to the sodium salt and exhibits equal or better efficiency as a radiostrontium binder.

4. Investigations of the Environmental Radiochemistry Unit

Although exposure of humans to radioactive materials in the environment may result from external irradiation, inhalation, and ingestion, the greatest absorbed dose is likely to be produced by ingestion. Because of ecologic conditions and the chemical properties of radioisotopes of strontium, cesium, and iodine; milk, meat, and their processed products represent the more important components of the human diet which contribute to radionuclide exposure. Public health measures to decrease human exposure from these foods may involve actions affecting normal production, processing, distribution, and use of dairy and meat foods. These measures generally are designed to be employed at the direct "product to man" level as indicated by steps I, II, III, and IV in the food chain chart (Figure 39).

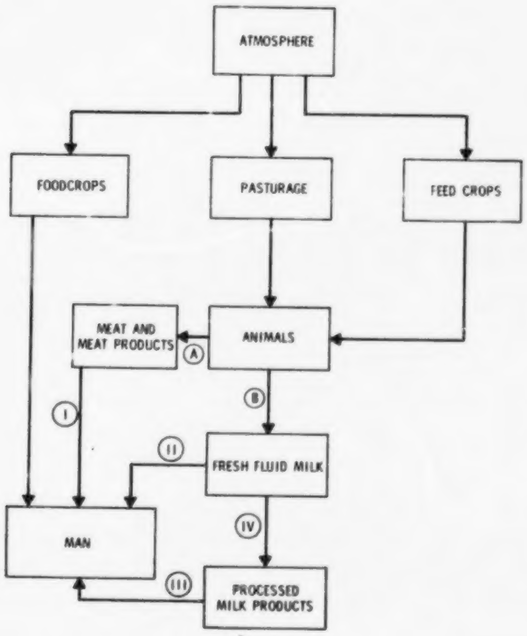

ATMOSPHERE
FOODCROPS
PASTURAGE
FEED CROPS
MEAT AND MEAT PRODUCTS
Ⓐ
ANIMALS
Ⓑ
Ⓘ
Ⓘⓘ
FRESH FLUID MILK
ⒾⓋ
MAN
ⒾⒾⒾ
PROCESSED MILK PRODUCTS

Figure 39. Radionuclide Transport from Atmosphere Through Food Chain.

The Environmental Radiochemistry Unit seeks to prevent or decrease the entrance of radionuclides into the food chain at the prior "animal to food" level, as indicated at A and B (Figure 39). This would eliminate or diminish the necessity for handling milk and other foods to remove contaminating radionuclides, and thereby reduce human radiation exposure through ingestion.

One way to decrease the entrance of radionuclides into the food chain is to divert dietary radionuclides in the animal from milk and meat to urine and feces. The Unit has investigated the chemical and physical properties of several substances to determine their applicability as radionuclide binding agents. Such substances, when fed to domestic ruminants, bind the radionuclides to mineral particles in the animal gut so that they cannot be absorbed through the intestinal wall and will pass out in the feces.

A second method of reducing radionuclides in the food chain involves the biochemical and physiological mechanisms of mammary secretion. Of particular interest are the secretions involving radioactive iodine or cesium. Through an understanding of the fundamental processes, a physiological model may be developed which would be useful in (a) estimating milk radionuclide levels following environmental releases of radioactivity, (b) theoretically evaluating certain proposed countermeasures, and (c) evaluating observed variations of mammary radionuclide secretions both within and among different animal species.

The research of the unit involves in vitro laboratory procedures as well as activities in vivo which employ a wide range of laboratory and domestic animal species including rats, guinea pigs, chickens, goats, miniature swine, and cows.

a. In Vivo Binding Materials

J. Barth, D. G. Hazzard, T. J. Withrow, B. H. Bruckner

Two clay materials, verxite flakes and Belle Fourche bentonite, have shown promise as in vivo binding agents for radioisotopes of the alkali and alkaline-earth metals. Experiments using verxite flakes were performed on 16 goats. Verxite flakes comprised about 10% of the grain ration (approximately 3% of total ration) of half of the animals. Each morning the animals were given either strontium 85 or cesium 134 per os at levels which ranged between 0.2 and 0.6 μCi. The goats were milked twice daily and total 24-hour collections of urine and feces were made. Portions of all samples were counted using a gamma scintillation spectrometer. The verxite-treated animals receiving cesium 134 had a more rapid rate of radioisotope excretion than did the non-treated animals. The percentages of the total body clearance of cesium 134 occurring during the dosing periods approximated 85% and 60%, respectively, for the treated and non-treated groups. The general trends of the three components measured, when expressed as percentages of the daily ingested doses of cesium 134, were in the magnitude of 7-fold decrease in milk and urine and a 2 1/2- to 3-fold increase in fecal excretion with the addition of verxite. There were no consistent differences between the treated and non-treated animals receiving strontium 85.

In collaboration with the SWRHL 16 lactating Holstein cows were used to measure the effects of four levels of verxite on cesium 134 metabolism. The results of this study appear to substantiate earlier goat experiments. The cows consuming feed containing about 3% verxite flakes showed a cesium level in the milk more than 85% lower than the control animals. It likewise appears that the inclusion of the verxite had no effect on the major mineral levels of milk.

Studies with Bell Fourche bentonite as a binding agent also showed promise. Natural Belle Fourche bentonite was incorporated in feed and then fed to goats housed in metabolic cages (Figure 40). Urine, feces, blood, and milk were analyzed to determine the binding qualities of the clay in the digestive tract. These goat studies substantiated the in vitro laboratory work (see p. 98) showing a relatively high reduction in the level of radiocesium in milk when the diets included natural Belle Fourche bentonite.

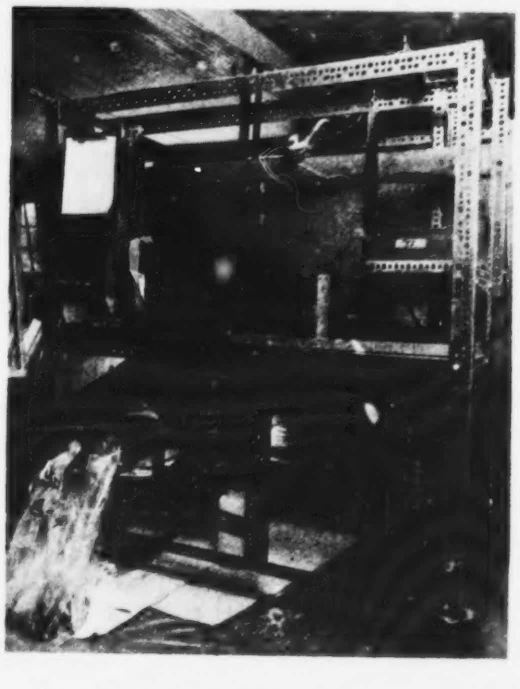


Figure 40. Metabolic Cages Used to House Goats in Radionuclide Binding Feeding Trials.

In comparable feeding experiments, laying hens administered strontium 85 and cesium 134 and fed dietary verxite flakes showed reduced cesium levels in the egg shells and yolks. Marked reductions were also observed in the egg white. Strontium levels in eggs, however, were not appreciably altered by verxite feeding.

The polysaccharide alginic acid binds strontium in monogastric animals, but its effect in ruminants is not known. It may react similarly in the ruminant gut provided the bacterial enzymes present in the rumen do not destroy it. To determine alginate in body fluids, a sensitive quantitative test for alginate was developed. The procedure is an extension of a qualitative test for alginate and compares the transmittance curves of standard Night Blue solutions with those of similar solutions in which alginate has been precipitated. The test is relatively accurate in aqueous solutions containing moderate or high concentrations of alginate. Work is continuing to improve the accuracy and specificity of the procedure in very dilute solutions and in those containing proteins or other polysaccharides.

Results of preliminary trials in which sodium alginate was fed to goats indicated some binding effect on strontium 85 in the gut. Further work with a larger number of animals under more controlled conditions has been concluded and the data are being evaluated. Sodium alginate apparently has no significant effect on the binding of cesium 134 in vivo in lactating goats.

b. In Vitro Ruminant Digestion

J. Barth, B. H. Bruckner

Ruminant digestive processes were simulated in the laboratory to screen various materials to determine their value as possible binding agents for radionuclides. The "artificial rumen" consists of flasks that are maintained in a constant-temperature shaker bath and supplied with carbon dioxide (Figure 41). The flasks contain rumen juice obtained from fistulated cows at the Dairy Research Unit, U. S. Department of Agriculture at Beltsville, Maryland. The substance to be evaluated is added to the flask containing the rumen juice, the pH is adjusted, and the flask incubated to simulate the digestive processes in the rumen. After the incubation period, pepsin, HCl, and salt are added and the pH adjusted to convert the artificial rumen to a simulated abomasum (fourth stomach). Following the gastric digestion period in the simulated abomasum, bile, pancreatin, and other enzymes are added and the pH adjusted again to approximate the conditions in the jejunum, the anterior portion of the small intestine. During the simulated digestive processes, samples of the contents are removed for chemical or radiochemical analyses. The procedure is economical in time, labor, and materials, and can serve to screen materials and procedures which would be quite costly in ruminant animals, as a first evaluation step.

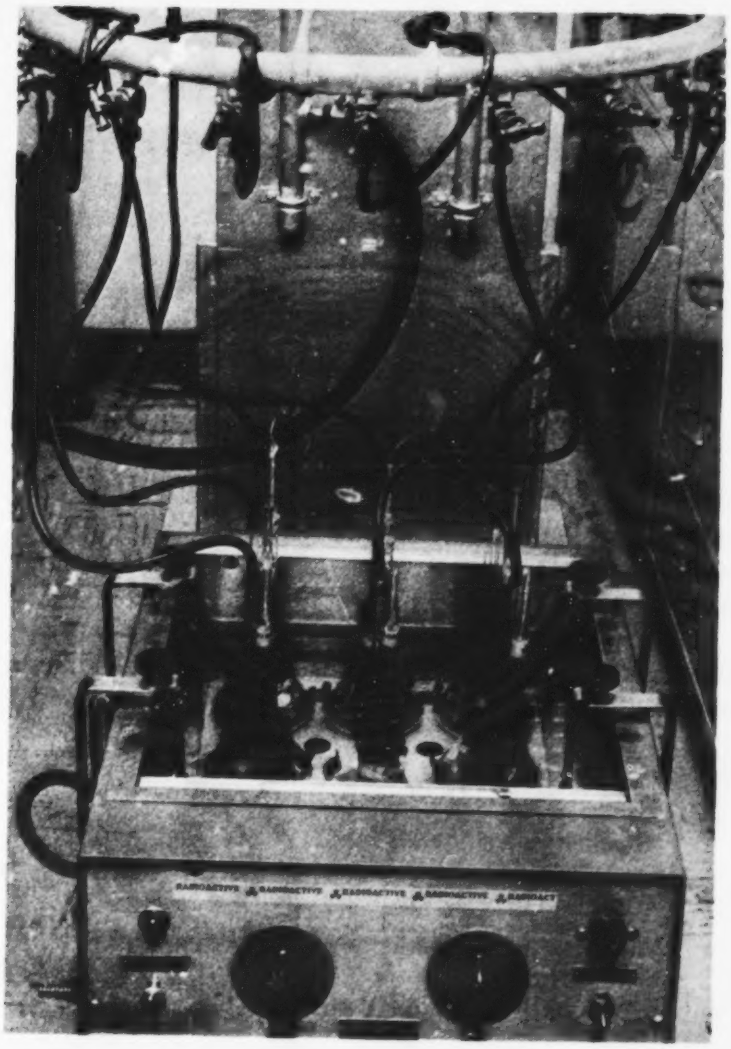


Figure 41. "Artificial Rumen" Used in Screening Studies.

During the year, both the natural and the hydrogen forms of the clays Belle Fourche bentonite, Aberdeen bentonite, and EPK kaolin were evaluated in the apparatus to determine their ability to bind cations of strontium, calcium, magnesium, potassium, and sodium. Other trials evaluated their ability to bind cesium 134. Although none of the clays bound Sr, Ca, Mg, K, or Na to any significant extent, both natural Belle Fourche bentonite and the hydrogen form of Aberdeen bentonite showed promise in these trials as binding agents for cesium 134. Subsequent studies indicated that the radionuclide was not associated with the rumen microflora or other sediment to any great degree.

c. Reduction of Levels of Fission Products in Milk

J. Y. Harris

Studies have been carried out with goats to evaluate the influence of various dietary factors on radionuclide levels in milk. In preliminary studies an inverse relationship was observed between the levels of non-iodized salt consumed ad libitum by goats and the levels of iodine 131 in their milk after oral tracer doses. This was followed up by controlled salt intake experiments with rats, and later by similar studies with lactating goats. In the goat studies, sodium chloride consumption of 0.4 and 1.1 g/kg body weight per day increased the urinary iodine-131 clearance rate, increased the urine to milk ratio, and reduced the total milk iodine-131 excretion by 25 to 46%.

Calcium, iron, and the anion exchange resin Dowex 1x10 were evaluated for their potential to reduce iodine absorption from the gastrointestinal tract of goats. Only the resin showed a significant influence on iodine metabolism. Resin-treated goats had 51% less iodine 131 in their milk, 43% less in their urine, and 277% more in their feces than control goats. In addition, the treated animals had a 14-hour biological elimination half time (extra thyroidal iodine 131) compared to 21 hours for the controls.

The cation exchange resin Dowex 50Wx8 was fed to lactating goats dosed with cesium 134 or strontium 85. The treated goats received 55 grams of the strong acid resin daily which had no significant influence on the cesium or strontium metabolism.

d. Nutritional Evaluation of Processed Milk

D. G. Hazzard, B. H. Bruckner

The Environmental Radiochemistry Unit has begun feeding trials of milk that was processed to remove radioactive iodine and strontium (see page 74). Palatability studies in weanling rats demonstrated no significant differences in acceptability of processed milk and control milk. The experimental and control animals showed no significant differences in amounts of milk consumed, in weight gains over the same time period, and in general appearance. All the values were within normal limits. Earlier trials on milk subjected to the cationic resin removal process demonstrated the nutritional acceptability or the product.

Currently in progress are feeding and evaluation trials in young miniature pigs (Figure 42). These are designed to measure the nutritional quality of the milk for relatively short-term emergency feeding.

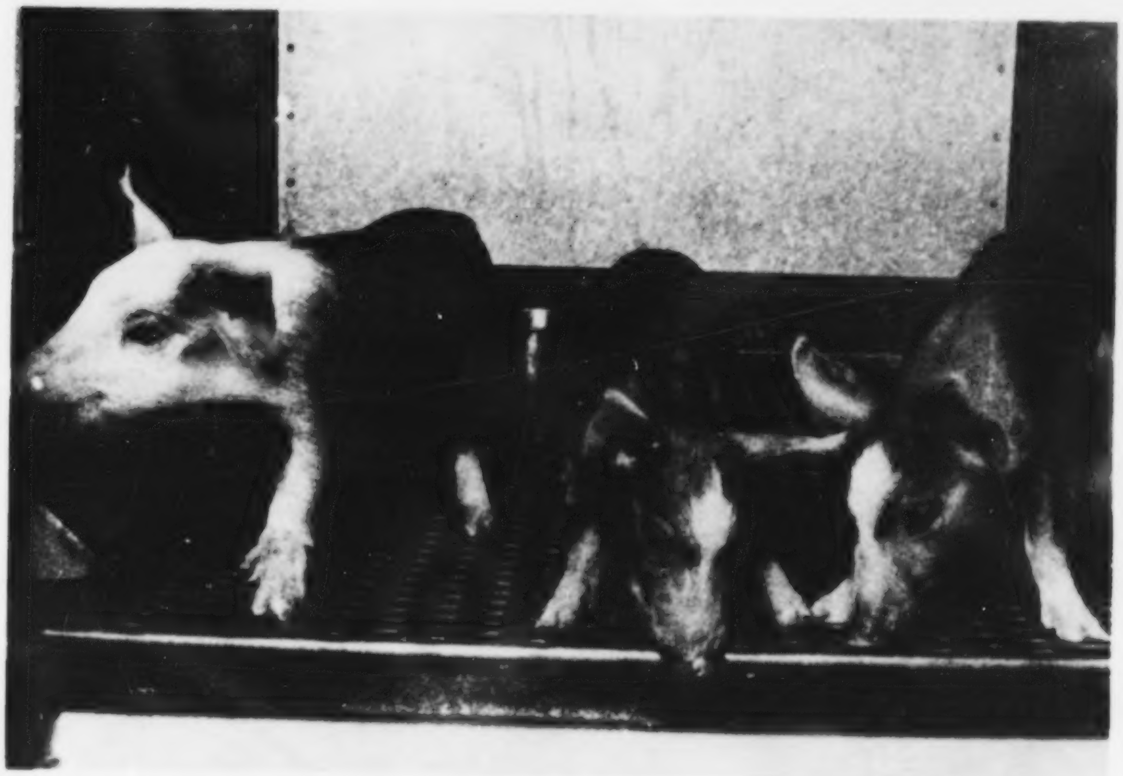


Figure 42. Miniature Swine Used in Feeding Trials of Decontaminated Milk.

5. Terrestrial Nuclide Cycling

H. Krieger, S. Cummings, F. Burmann, J. Hasuike

a. Deposition and Uptake of Strontium 90 and Cesium 137 in an Established Pasture

The accumulation of strontium 90 and cesium 137 from fallout and their transfer from precipitation and soil were measured in an established bluegrass pasture on Fox soil (Figure 43). From these results the average percent uptake by bluegrass from a Fox soil for strontium 90 and cesium 137 was predicted to be 0.09 and 0.009, respectively. The average transfer coefficients predicted for deposition on grass from fallout were 12% for strontium 90 and 5.7% for cesium 137. These coefficients were within the wide range of values cited in the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) Report.

Figure 43. Field Plot for Deposition and Uptake Studies of Strontium 90 and Cesium 137.

b. Disappearance Half-Time Study

Information on the length of time cesium 137 and strontium 90 will remain on an established pasture following a single nuclear event will help to confirm the limits suggested in the Federal Radiation Council Report No. 7.

Sod and soil, representative of the Wisconsin milk shed, were placed in three 20- by 80-inch plots. Two of the plots were terraced in sloping concrete ponds; the third plot was adjacent to them

(Figure 44). The terraced plots were equipped with electronically controlled aluminum covers that rolled over them to protect the grass at the first indication of precipitation (Figure 45).

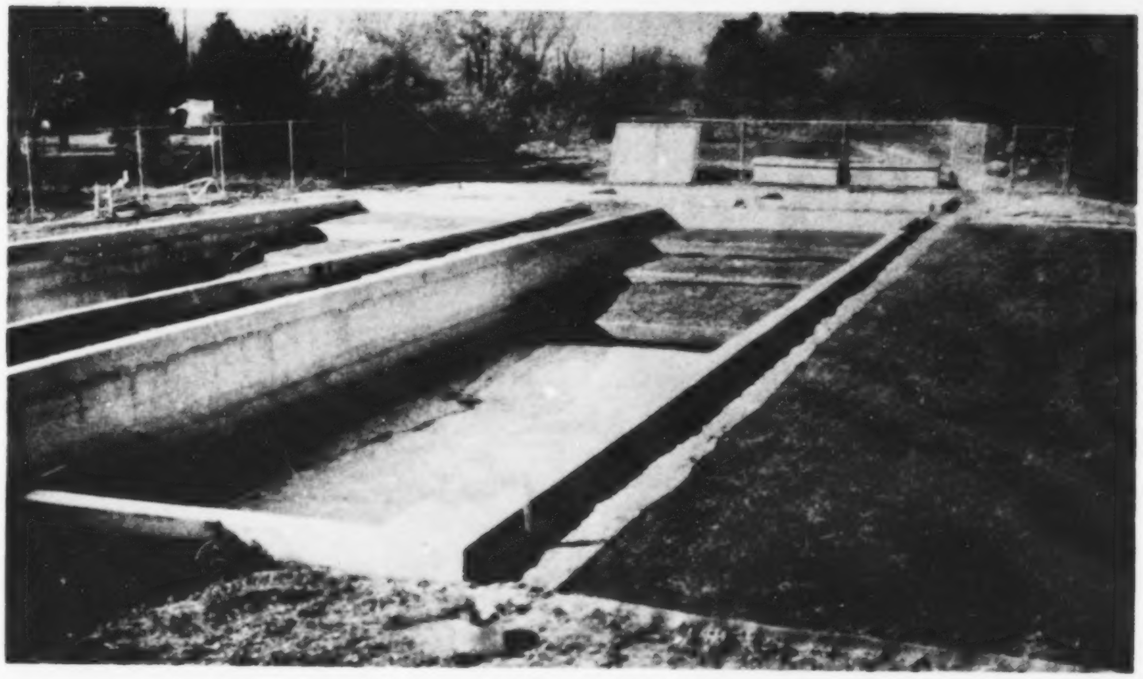


Figure 44. Disappearance Half-Time Study Areas Showing Terraced Ponds and Adjacent Plot.

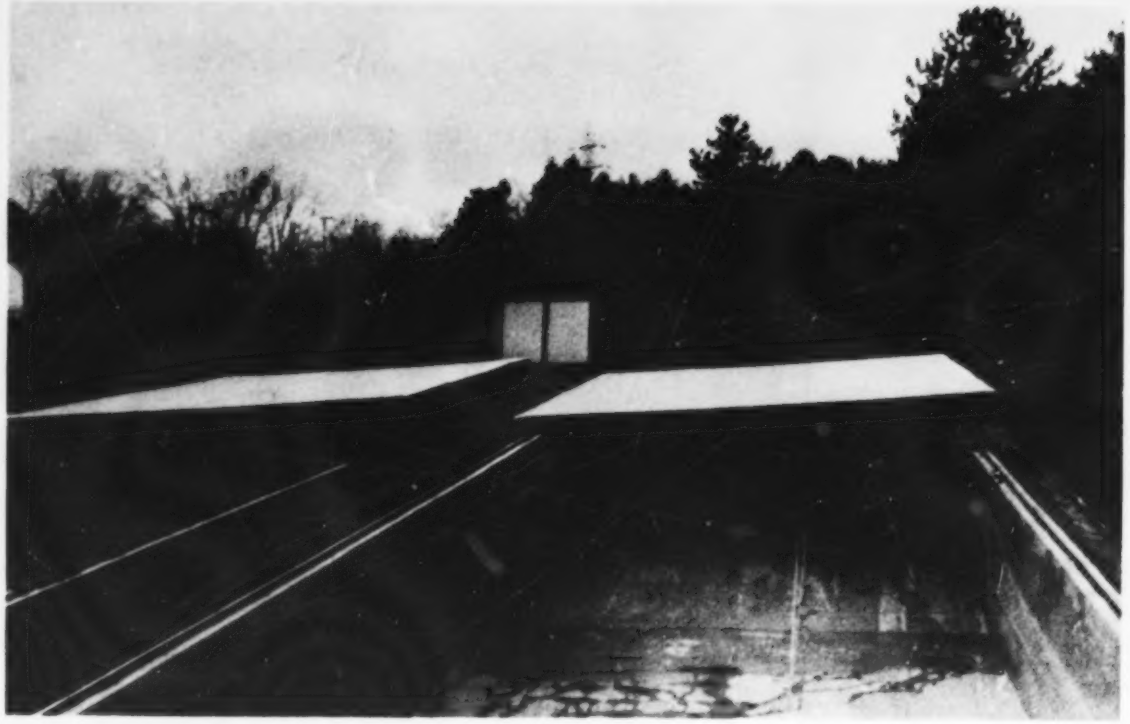


Figure 45. Aluminum Covers That Protect Terraced Plots From Precipitation.

After lying dormant through the fall and winter, the plots were sprayed in the early spring with water containing strontium 85 and cesium 134. Grass samples from each section, which were sampled using grid coordinates, indicated the decrease in activity with time. The parameters of grass height and effect of precipitation were considered in the calculations of the disappearance half-time of these nuclides.

c. Ruthenium Oxidation States

The radioactive transfer values and organs of maximum concentration postulated by the International Commission on Radiological Protection are derived from studies relating to a specific chemical form of a radionuclide. Since radionuclides may exist in several oxidation states, the recommended values must be confirmed or corrected in terms of each state. Five oxidation states of ruthenium 106 are being investigated and prepared for administration to cats in several substates.

In a preliminary investigation, the five states were orally administered to cats. Body burdens and organs of maximum concentration were determined. The tissues were analyzed to determine the activity that remained in them after the first elimination by the animals. Two states showed 2% transfer from gastrointestinal tract to blood; 5% for the third, 9% for the fourth, and 12% for the fifth.

6. Radioactivity in Tobacco and Tobacco Smoke

S. C. Black, E. W. Bretthauer

The alpha activity in tobacco and the extent to which this activity may represent a hazard to the smoker are being investigated. Both direct alpha dosage and indirect or synergistic effects are being explored. Methods of reducing the hazard are also to be explored. Twenty-nine brands of non-filter cigarettes, domestic and foreign, and cigars and pipe tobaccos have been analyzed for polonium 210. These samples will also be analyzed for lead 210 and radium 226.

A referee sample consisting of 25 pounds of cigarette tobaccos has been accumulated. Leaf tobacco samples from 13 foreign countries (20 different varieties) have been obtained for analysis. Comparisons between smoking machines and human smokers have revealed that cigarette filters are relatively inefficient for removing polonium, and that the concentration of polonium in mainstream smoke increases directly with puff size. Theoretical calculations suggest that a heavy smoker may receive an alpha dose to his lungs which is as much as 100 times the background alpha.

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APPENDIX A

RESEARCH BRANCH ORGANIZATION TABLE

RESEARCH BRANCH UNITS IN VARIOUS LABORATORIES

RESEARCH BRANCH
Arthur H. Wolff, Chief
Albert W. Hilberg, Deputy Chief

RADIOBIOLOGY SECTION
A. K. Davis, Chief
EPIDEMIOLOGY SECTION
Stella Booth, Acting Chief
BIOMETRICS
Edward S. Weiss, Chief
ENVIRONMENTAL SCIENCES SECTION
Ronald E. Bales, Chief
John L. S. Hickey, Deputy Chief

RADIOLOGICAL HEALTH RESEARCH ACTIVITIES, CINCINNATI, OHIO
- Bernd Kahn, Chief
- Gerald Karches, Assistant Chief
- RADIONUCLIDE METABOLISM PROGRAM
  - Jerry F. Stara
- NUCLEAR MEDICINE PROGRAM
  - Henry N. Wellman
- BIOENVIRONMENTAL RADIATION TRANSPORT STUDIES
  - Herman Krieger
- RADIOMETRICS SUPPORT
  - Byron Branson
- HUMAN EXPOSURE FROM NATURAL RADIONUCLIDES
  - R. L. Blanchard
- INTRALABORATORY QUALITY CONTROL
  - Harry E. Kolde
- COMMUNITY ENVIRONMENTAL RADIATION EXPOSURE STUDIES
  - Richard K. Stoms
- MILK AND FOOD CHEMISTRY
  - Jeptha E. Campbell
  - Gopala K. Murthy

TWINBROOK LABORATORY, ROCKVILLE, MARYLAND
- William A. Mills, Officer-In-Charge
- RADIATION ONCOLOGY AND PATHOLOGY
  - Norman C. Telles
- RADIATION PHYSICS
  - Harry D. Youmans, Jr.
- CYTOGENETICS
  - Wellington Moore, Jr.
- BIOPHYSICS
  - Moris L. Shore
- ENVIRONMENTAL RADIOCHEMISTRY
  - Benjamin H. Bruckner

SOUTHEASTERN RADIOLOGICAL HEALTH LABORATORY, MONTGOMERY, ALABAMA
- Melvin W. Carter, Officer-In-Charge
- ENVIRONMENTAL SCIENCES
  - Jesse P. Walker, Jr., Samuel L. Cummings, Arthur H. Garrett

NORTHEASTERN RADIOLOGICAL HEALTH LABORATORY, WINCHESTER, MASSACHUSETTS
- Dade W. Moeller (Officer-In-Charge, Retired)
- Morgan S. Seal, Officer-In-Charge
- THOROTRAST STUDY
  - David E. P. Fitzpatrick

COLLABORATIVE RADIOLOGICAL HEALTH LABORATORY, FORT COLLINS, COLORADO
- R. John Garner, Director
- James N. Shively, Senior PHS Investigator

SOUTHWESTERN RADIOLOGICAL HEALTH LABORATORY, LAS VEGAS, NEVADA
- Oliver R. Placak, Officer-In-Charge
- BIOENVIRONMENTAL RESEARCH PROGRAM
  - Delbert S. Barth
  - PHYSICAL SCIENCES GROUP
    - Stuart C. Black
  - BIOLOGICAL SCIENCES GROUP
    - Ronald E. Engel

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